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PRINCIPAL INVESTIGATOR: Lawrence P. Burgess, M.D.

CONTRACTING ORGANIZATION: University of Hawaii
Honolulu, HI 96822-2303

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Lawrence P. Burgess, M.D.

E-mail: lburgess@hawaii.edu

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University of Hawaii
Honolulu, HI 96822-2303

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14. ABSTRACT

This effort helped to support the establishment of a Joint Clinical Research Center (JCRC) in Thailand in a partnership with the Royal Thai Army (RTA), the Armed Forces Research Institute of Medical Science (AFRIMS), and the University of Hawaii. The Center will provide a vehicle for the study of infectious diseases (including bioterrorism) with full patient, laboratory and animal facilities. There remains significant difficulty in providing timely research when the majority of affected populations for diseases live on foreign soil. This center is fully integrated with broadband medical networking and clinical informatics assuring international communication and local/regional access to affected patient populations. UH provided research collaboration and administrative personnel to the Center. In an additional proposal modification, UH provided advanced simulation training to the annual Asia Pacific Military Medical Conference held in Vietnam in an effort to develop stronger associations throughout Southeast Asia for expanding infectious disease research interests in the region.

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Table of Contents

Cover……1

SF 298……..2

Introduction……...4-5

Body…….5-8

Key Research Accomplishments……8-9

Reportable Outcomes……..9

Conclusions……9-10

References……..10

Appendices……11-120

A-1: UH-PMK NeuroAIDS Study 001: Predictors of Neuro-cognitive Decline and Survival in HIV-infected Subjects (A Pilot Study)……12-47

A-2: Hawaii AIDS Clinical Research Program……..48-51

A-3: Hawaii AIDS Clinical Trials Unit……..52-111

B-1: APMMC Hanoi May 9-13, 205, Agenda (Simulation and Training)……112-113

B-2: Abstract for APMMC Simulation Training……114-115

B-3: International Military Medical Simulation Symposium After Action Report……116-120

Introduction

In an era of dramatically increased travel, rapid natural (and even engineered) manipulation of infectious agents, as well as security concerns related to bioterrorism, a new means of testing and evaluation for vaccine and antibiotic therapy is desperately needed. While both the DOD and NIH have been long focused on this problem, there remains significant difficulty in providing timely research when the majority of affected populations for these diseases live on foreign soil. To address this problem, the ideal scenario would consist of a foreign-based Clinical Trials center fully integrated with the most advanced technologies in broadband medical networking and clinical informatics assuring local and regional access to affected patient populations and seamless integration with state of the art US research methods. Beyond technology, new models of integrating government agencies, non-governmental organizations and private industry could be tested in such a setting. A US certified laboratory with a large animal lab including primates would be a necessity to support such a clinical trials unit, as well as a close working relationship with a friendly host nation's medical personal. The Center should also have strong affiliations with one or two universities conducting both basic science and clinical research at the Center. The Center should also have broadband links to the US for transfer of data, and collaboration with ongoing genomics and proteomics research in the field.

With this in mind, the objectives of this funded effort were to: 1) identify locations and partners where such activities might be conducted, 2) outline structure of partnership and funding from collaborating organizations, 3) provide seed funding to the initiative, 4) develop alternative and traditional funding sources through government and private industry.

The most recent award (200K) provided funding to support a Joint Clinical Research Center (JCRC) with partners identified as the Royal Thai Army (RTA), the Armed Forces Research Institute of Medical Science (AFRIMS), and the University of Hawaii. A pre-proposal planning meeting was held in June of 2004, which helped to outline the activities for the following year (including the activities summarized in this annual report).

In addition to the effort described above, an additional modification was added to the existing proposal to expand relationships with nations in Southeast Asia (SEA) which will help foster bioterrorism related infectious disease research in Thailand and SEA in general. UH has a growing relationship with the Asia Pacific Military Medical Conference (as attendees and presenters). The conference assembles all SEA military medical officers for one week annually and provides an outstanding opportunity to bring advanced simulation based training to the attendees (while also providing a more significant presence for UH in SEA). The goal of this additional effort was to provide two days of didactic sessions followed by a day-long training session for SEA medical officers and bring the conference to a new level. The team delivering the program to the

conference consisted medical leaders of the Winter Institute for Simulation, Education and Research (WISER) of the University of Pittsburgh Medical Center and UH. The ultimate goal in the future is to become an annual event at APMMC where UH can develop stronger associations throughout SEA, thus making it more capable of expanding its infectious disease research interests in the region.

With this in mind, the objectives of this grant modification was 1) for UH to partner with WISER to combine its on-line/live training curriculum with the simulation training from the University of Hawaii (UH) to develop an advanced simulation-based training for the APMMC and 2) conduct the advanced simulation-based training on-site during the 2005 APMMC held in Vietnam.

Body

The following is a description of the research accomplishments for the two efforts associated with this award: 1) Joint Clinical Research Center and 2) Advanced Simulation-based Training for APMMC:

Joint Clinical Research Center

The accomplishments are associated with each task in the Statement of Work. The tasks from the Statement of Work are as follows:

1. Identify locations and partners for forming a Clinical Trials Center in emerging infectious diseases,
2. Outline the structure of partnerships and funding from collaborating organizations for a Clinical Trials Center,
3. Provide seed funding to the initiative,
4. Develop alternative and traditional funding sources through government and private industry.

The most recent award provided funding to support a Joint Clinical Research Center (JCRC) with partners identified as the Royal Thai Army (RTA), the Armed Forces Research Institute of Medical Science (AFRIMS), and the University of Hawaii. The planning meeting that was held in June of 2004 in Thailand helped to outline the activities that followed in 2005.

In 2005, we funded through this grant a 10% FTE UH faculty member (George Watt, M.D.), who is a former AFRIMS Department Chief. Dr. Watt is fluent in the Thai language and lives in Thailand. He is a world infectious disease authority on Leptospirosis. Through this funding, Dr. Watt was able to provide important administrative time to help establish an activate the JCRC.

The University of Hawaii's HIV working group also began the initiation of a clinical trial (NeuroAIDS Study 001) in conjunction with the Center, looking at neurological complications of HIV/AIDS (see Appendix A). Dr. Watt assisted administratively in the

process, so that the Center could support such a study. In addition, a part-time nurse coordinator was hired to help and administrate the Center. For assigned time from this grant, both Dr. Watt and the nurse coordinator did not conduct research.

The NeuroAIDS study is a cross-sectional NeuroAIDS protocol that was designed as a joint collaborative attempt between researchers at the University of Hawaii, Phramongkutlao (PMK) Hospital and AFRIMS. The study opened in August 2004, and in December of 2005 completed its initially determined target accrual of 45 subjects.

Video-teleconferencing capabilities in place at Leahi Hospital, Honolulu, Hawaii and PMK, Bangkok, Thailand, has been invaluable for the purposes of developing the international infrastructure in Bangkok. Teleconferences to discuss various aspects of the infrastructure and training/research activities occur between Honolulu and Bangkok faculty members and program staff on a weekly basis on Thursdays 2:30 pm Hawaii Time (Friday 7:30 am Bangkok time).

In 2005, a new partnership with HIVNAT (HIV Netherlands Australia Thailand Research Collaboration) began. The developing research infrastructure will operate under the name SEARCH. A SEARCH website has been added under the Hawaii AIDS Clinical Research Program website: http://www.hawaii.edu/hacrp/search.htm. SEARCH partners include PMK, U.S. AFRIMS, HIVNAT and UH (see Appendices A-2 and A-3).

SEARCH research/training international infrastructure has lead to the following grant proposals/projects:

(Funded) **Macrophages, HAART, And HIV-1 dementia in Thailand**. (1 R21 MH072388-01) V. Valcour PI ***Funded, July 2004***
This awarded funding supports the longitudinal aspects of the original NeuroAIDS study; $300,000 total direct funding over 2 years.

(Pending) **Hawaii AIDS Clinical Trials Unit**, response to RFA-AI-05-002. C. Shikuma Proposed PI.
The research infrastructure developed in Bangkok was incorporated as part of this grant proposal for HIV vaccine and Optimization of Care clinical trials. If successful, total direct costs for UH is $2.3 million/year x 7 years. Review of grant is pending.

(Funded) **International HIV/AIDS Training Center** (Gilead Pharmaceutical)
This training center will be designed to train SE Asia civilian physicians in HIV/AIDS care and management. Initial group of trainees is scheduled for early 2006. Funded for total cost of $100,000.

(Funded) **President's Emergency Plan for AIDS Relief (PEPFAR)** (via Department of Defense CoE)
Funding will support training of 8-12 Vietnamese physicians in HIV care and management/year. Direct costs of approximately $210,000/ year x 5 years.

(Pending) **Safety, Tolerabilitiy and Immunogenicity of ACAM3000 Modified Vaccina Ankara (MVA) Small Pox Vaccine in HIV-Seropositive Subjects who are Vaccinia Naïve** (Acambis Pharmaceuticals) Review of proposal for SEARCH to open in Bangkok pending. Direct costs of approximately $200,000 total for study.

(Awarded) **HIV/AIDS Regional Training and Research Center in Asia** (Hui)
The funds support the University of Hawaii efforts to develop training and research infrastructure in HIV in Asia. Direct costs of approximately $300,000 x one year.

Advanced Simulation-based Training for APMMC:

The accomplishments are associated with each task in the Statement of Work. The tasks from the Statement of Work are as follows:

1. Combine WISER's on-line/live training curriculum with the simulation training from UH Telehealth Institute to develop an advanced simulation-based training event for the APMMC.
2. Conduct the advanced simulation-based training during the APMMC held in Vietnam.

The Asia Pacific Military Medicine Conference (APMMC) is a US Army Pacific (USARPAC) program conducted in support of the Pacific Command (PACOM) Theater Security Cooperation Plan (TSCP). The conference engages 25-30 Asia-Pacific international Military Medical departments in a program of scientific exchange during a 5 day conference. APMMC has been conducted annually for 15 years. Topics presented by delegates are of general interest with a focus on operational medicine, military medical technology, disaster relief and humanitarian assistance, infections disease, HIV, and environmental medicine. Over 200 presentations are made during this English language conference.

UH combined efforts with the WISER Institute at the University of Pittsburgh Medical Center to use its online/live training curriculum with the simulation-based training already existing at UH. An advanced simulation-based training event (Simulation Symposium) was developed with accompanying agenda and abstract for the conference (see Appendices B-1, B-2, B-3). The Simulation symposium was comprised of two didactic sessions including real-time demonstration simulator orientation, and a one-day simulation hands-on practicum, focused on provision of simulation experience to the co-hosting Vietnamese Army medical personnel. English to Vietnamese translated written documents including medications, and scenario algorithms were utilized for the simulation practicum.

Sessions were attended by General Officers from the US, India, Malaysia, Vietnam, Australia, Cambodia, Laos, Singapore, Thailand, and other nations. Surgeons General from multiple nations attended.

Simulation didactic sessions were well attended, exceeding attendance expectations and capacity of the facilities (the facility could seat 60 people, but this event exhibited "standing room only" attendance). The integrated presentations from academic and military programs provided a broad overview of simulation training, military relevance, and technical capability. Attendees engaged the faculty in discussion. Significant interest in development and/or enhancement of simulator training capacity was expressed by senior medical officers from Australia, Singapore, Vietnam, India, and Thailand. Simulation based medical education concepts across multiple domains were presented. Cognitive-behavioral learning concepts, technical details, logistics, and faculty development were included in the two days of didactic presentations. Demonstration mannequin systems were utilized in several of the presentations.

Simulation Practicum sessions were conducted utilizing standard US based training scenarios. The mannequin technical systems were flawless. Most participants were familiar with the basic clinical concepts presented; none had previous simulator experience. These sessions included rotations through three mannequin based scenario stations and one computer-based simulation program, Micro-Sim®. The practicum sessions were the highlight of the program. The sessions facilitated direct and substantive student-teacher interaction. This type of direct interaction within the context of medical problem-solving and simulated procedures was entirely novel for participants. The educational processes, which were demonstrated, were enthusiastically received by all participants. Program coordinators observed active participant engagement across all domains of the program, including cognitive, skill development, and transcultural adaptive attitudes. Students enthusiastically accepted Certificates of Participation at the conclusion of the program.

In Vietnam the director of the 103 Military Hospital recalled the Director of the Military Medical Academy to review the simulation program. This high level review resulted in a specific request to consider simulation training in future US/Vietnam Military to Military programs.

Key Research Accomplishments

The following is a bulleted list of key research accomplishments emanating from this effort:

- The University of Hawaii provided support toward the establishment of a Joint Clinical Research Center (JCRC) in Thailand by funding a 10% FTE UH faculty member (George Watt, M.D.), who provided important administrative time to the JCRC. In addition, a part-time nurse coordinator was hired to help and administrate the Center.

- The University of Hawaii's HIV working group began the initiation of a clinical trial (NeuroAIDS Study 001) in conjunction with the Center (a cross-sectional NeuroAIDS protocol that was designed as a joint collaborative attempt between researchers at the University of Hawaii, Phramongkutlao (PMK) Hospital and

AFRIMS -- see Appendix A). For assigned time from this grant, both Dr. Watt and the nurse coordinator did not conduct research.

- A new partnership with HIVNAT (HIV Netherlands Australia Thailand Research Collaboration) began, operating under the name SEARCH. A SEARCH website has been added under the Hawaii AIDS Clinical Research Program website: http://www.hawaii.edu/hacrp/search.htm. SEARCH partners include PMK, U.S. AFRIMS, HIVNAT and UH (see Appendices A-2 and A-3). SEARCH research/training international infrastructure has lead to six grant proposals/projects (see previous section).

- UH combined efforts with the WISER Institute at the University of Pittsburgh Medical Center to use its online/live training curriculum with the simulation-based training already existing at UH to develop an advanced simulation-based training event (Simulation Symposium) for the Asia Pacific Military Medicine Conference (APMMC) in Vietnam. The APMMC is a US Army Pacific (USARPAC) program conducted in support of the Pacific Command (PACOM) Theater Security Cooperation Plan (TSCP) (see Appendices B-1, B-2, B-3). The training symposium was successfully accomplished during the conference.

Reportable Outcomes

1. UH-PMK NeuroAIDS Study 001: Predictors of Neuro-cognitive Decline and Survival in HIV-infected Subjects (A Pilot Study).

(see report in Appendix A-1.)

2. The agenda, abstract, and after action report for the Simulation Training, Trauma Life Support activity for the APMMC, Hanoi (May 9-13, 2005).

(see Appendix B.)

Appendix B-1 contains the agenda of the event. The Simulation Training, Trauma Life Support activity for the APMMC took place May 9-13, 2005 in Hanoi. Appendix B-2 contains the abstract for the event. Appendix B-3 contains the after action report summarizing the event, listing the faculty and key contacts, analysis of the training success, conclusions and recommendations.

Conclusions

The third year of this effort was successfully completed. Through this effort important initial steps were made to increase research and collaboration between the US and SEA and establish crucial foundations to more effectively deal with bioterrorism or infectious diseases in the future.

Building on the established relationships between UH, PMK, and AFRIMS, this grant helped to provide supplemental funds to assist in forming a Clinical Trials Center in emerging infectious diseases at PMK. The location is unparalleled for the study of emerging infectious diseases. UH and PMK have grown closer together through its collaborative grants, and AFRIMS and PMK have been long-time collaborators. A UH association will also readily permit NIH funded studies to be conducted at the Center.

Although based on foreign soil, such a Center has distinct advantages, as it is being forged in a new era of advanced computing and telecommunications. The existing Internet2-type link provides "free" videoteleconferencing capability between investigators in Hawaii and Thailand, as well as other consultants in the US. This link also permits transfer of data to the UH's supercomputer for genomics or proteomics studies. The broadband linkage permits this Center to have a wealth of connectivity and computing power, but be located in the locale where patients are afflicted with the diseases of interest and can be studied more readily. The Center will provide a vehicle for the study of infectious diseases with full patient, laboratory (including basic science), and animal facilities. The current partnerships provide a unique opportunity to form this Center. TATRC's funding has been essential to provide administrative and infrastructure support to help stand up the Center as a collaborative entity

The opportunity through the Asia Pacific Military Medical Conference provided an outstanding method to bring advanced simulation based training to the SEA, while also providing a more significant presence for the University of Hawaii in SEA. Significant interest in development and/or enhancement of simulator training capacity was expressed by senior medical officers from Australia, Singapore, Vietnam, India, and Thailand. In addition, senior medical leaders in the Asia Pacific region expressed views that medical simulation training is a method with potential for integration with existing regional military training programs. Simulation training represents a novel method of transcultural medical education that should be further explored and expanded. We hope that this will become an annual event at APMMC, which will enable UH to develop stronger associations throughout SEA, thus making it more capable of expanding its infectious disease research interests in the region.

References

None

Appendices

A-1: UH-PMK NeuroAIDS Study 001: Predictors of Neuro-cognitive Decline and Survival in HIV-infected Subjects (A Pilot Study)

A-2: Hawaii AIDS Clinical Research Program

A-3: Hawaii AIDS Clinical Trials Unit

B-1: APMMC Hanoi May 9-13, 205, Agenda (Simulation and Training)

B-2: Abstract for APMMC Simulation Training

B-3: International Military Medical Simulation Symposium After Action Report

UH-PMK NeuroAIDS Study 001:

Predictors of Neuro-cognitive Decline and Survival in HIV-infected Subjects

A Pilot Study of the University of Hawaii (Honolulu, Hawaii, USA) – Phramongkutklao Medical Center (Bangkok, Thailand) NeuroAIDS Research Collaboration

In association with

University of Hawaii NeuroAIDS Specialized Neuroscience Research Program
UH NeuroAIDS SNRP
NINDS, NIH, USA
(Program Director: Cecilia Shikuma MD)
and
The Armed Forces Research Institute of the Medical Sciences (AFRIMS)
Bangkok, Thailand

Project Co-Chairs:	Victor Valcour MD (UH)) Samart Nidhinandana MD (PMK)
Project Laboratory Directors:	Bruce Shiramizu MD (UH) Col. Thippawan Chuenchitra PhD (AFRIMS)
Project Liaisons:	Jerome Kim MD (UH) Suwicha Chitpatima Ph.D. [Tim] (PMK) Cecilia Shikuma MD. (UH)

Table of Contents

List of Investigators and Key Contacts……..3
University of Hawaii Administrative Structure for Project…….5
Phramongkutklao medical Center Administrative Structure for Project…….6
Schematic Diagram of Data and Specimen Flow for Project……..7
Research Proposal…….....…...8
Specific Aims…….....…...8
Background and Rationale……..……9
Methods…….....11
Study Management and Key Personnel…….……11
Selection and Recruitment……...…..……12
Subject Evaluations Schema……..……....15
Table of Evaluation Schema…… 21
Statistical Concerns……...…….24

References……..24

Appendix
MRI Protocol (Appendix I) ……..…….....26
Lumbar Puncture Protocol (Appendix I)……..……..27
American Academy of Neurology HAD Criteria (Appendix II) ……..…28
Lab Processing Sheet (AppendixIII)…….……..30
Percoll and Advanced Flow Procedure (Appendix IV)…….…..32
Macrophage Isolation (Appendix V).....…….....34

List of Investigators and Key Contacts

University of Hawaii

University of Hawaii Project Chair:

Victor Valcour MD

Office of Neurology and Aging Research
Hawaii AIDS Clinical Research Program
John A. Burns School of Medicine
Sinclair 202, Leahi Hospital
3675 Kilauea Avenue
Honolulu, Hawaii 96816 USA
Phone: (808)-737-3012
Fax: (808)-273-1158
Email: Vvalcour@hawaii.edu

University of Hawaii – Project Laboratory Director:

Bruce Shiramizu MD

Hawaii HIV and Immunobiology Laboratory
Hawaii AIDS Clinical Research Program
John A. Burns School of Medicine
Young 5, Leahi Hospital
3675 Kilauea Avenue
Honolulu, Hawaii 96816 USA
Phone: (808)-737-2751
Fax: (808)-735-7047
Email: shira@hawaii.edu

Univ. of Hawaii Liaison to Phramongkutklao Medical Center:

LTC Jerome Kim MD

Director, Joint Asia Pacific HIV/AIDS Prevention Program
Tripler Army Medical Center
1 Jarrett White Road
Tripler AMC, Hawaii 96859-5000
Phone:(808)433-6513
Fax: (808)433-2707
Email: Jerome.kim@amedd.army.mil

University of Hawaii Investigators

Cecilia Shikuma MD

Program Director, Hawaii AIDS Clinical Research Program
John A. Burns School of Medicine
Young 5, Leahi Hospital
3675 Kilauea Avenue
Honolulu, Hawaii 96816 USA
Phone: (808)-737-2751
Fax: (808)735-7047
Email: shikuma@hawaii.edu

Silvia Ratto-Kim PhD
Hawaii AIDS Clinical Research Program
Young-B, Leahi Hospital
3675 Kilauea Avenue
Honolulu, Hawaii 96816
Phone: (808)- 441-1574
Fax: (808)735-7047
Email: silviak@hawaii.edu

Marianna Gerschenson PhD
Hawaii AIDS Clinical Research Program
Young basement floor, Leahi Hospital
3675 Kilauea Avenue
Honolulu, Hawaii 96816
Phone: (808)-441-1573
Fax: (808) 735-7047
Email: gerschen@hawaii.edu

List of Investigators and Key Contacts

Phramongkutklao Medical Center through Phramongkutklao Hospital

Phramongkutklao Medical Center
Project Chair:

Samart Nidhinandana MD

Assistant Professor of Medicine
Chief, Neurologic Division, Department of Medicine
Phramongkutklao Hospital
315/6 Rajvithee Rd
Bangkok 10400, Thailand
Phone: 02-354-7660 ext 93027
Fax: 02-354-7637
Email: msani@pmk.ac.th

Phramongkutklao Medical Center
Liaison to Univ. of Hawaii:

Suwicha Chitpatima PhD (Tim)
Director of International Affairs,
Phramongkutklao Medical Center
Assistant Professor of Biochemistry,
Phramongkutklao Medical School
315 Rajvithee Road
Bangkok 10400, Thailand
Phone: 66-02-354-7711 ext 90378
Fax: 66-02-354-7651
Email:s_tim_99@yahoo.com

Phramongkutklao Medical Center
Protocol Investigators:

Pasiri Sithinamsuwan MD

Division of Neurology
Department of Medicine
Pramongkutklao Hospital
315/6 Rajvithee Rd
Bangkok 10400, Thailand
Phone : 01-847-6034
Fax: 00-662-245-5526
Email : pasiri21795@yahoo.co.uk

Sataporn Thitivichianlert MD

Chief, Infectious Diseases
Department of Medicine
Phramongkutklao Medical Center
315/6 Rajvithee Rd
Bangkok 10400, Thailand
Phone: 66-02-354-7660 x93338
Fax: 66-02-644-4420
Email: sataporn th@hotmail.com

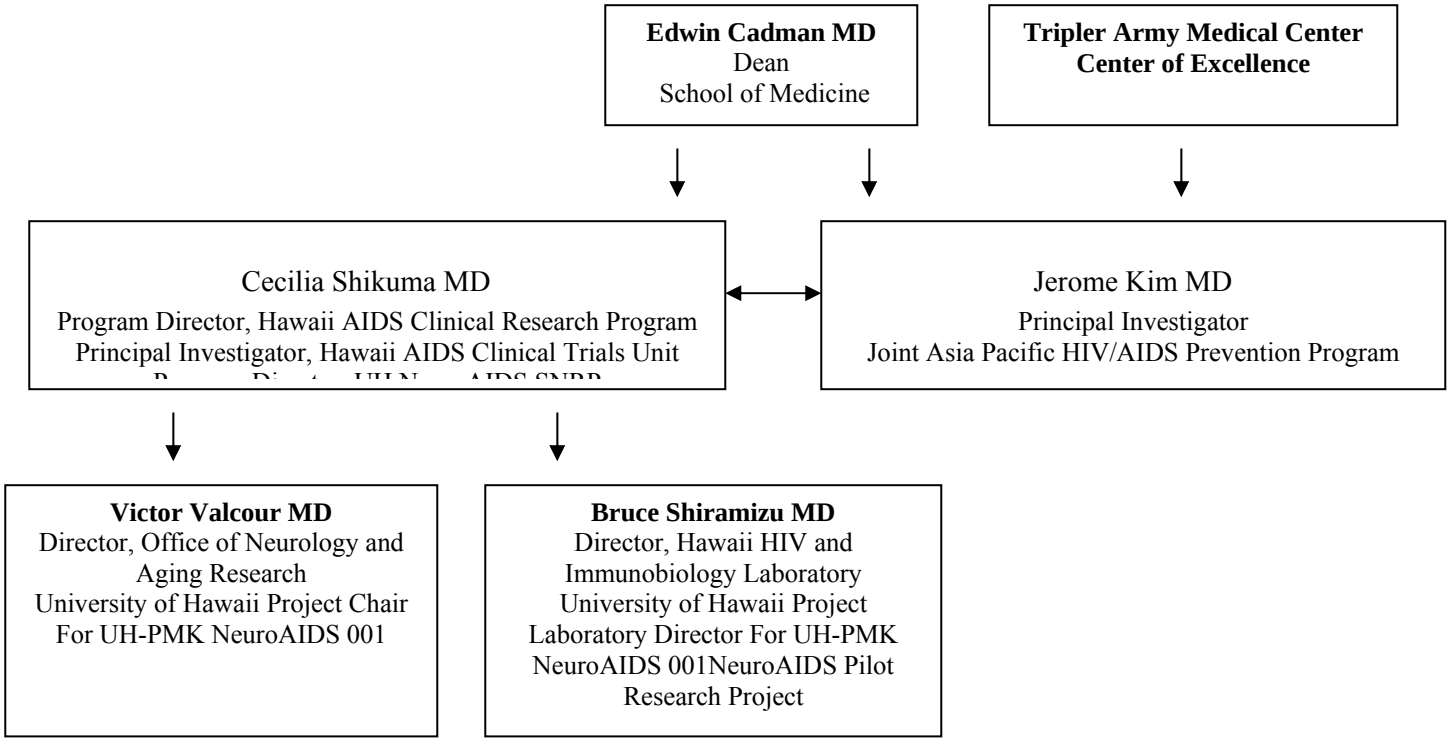
AFRIMS

Sorachai Nitayaphan, MD, PhD
Chief, Division of Research
Armed Forces Research Institute of the Medical Sciences (AFRIMS)
315/6 Rajvithee Rd
Bangkok 10400, Thailand
Phone 66-02-644-4888
Fax: 66-2-644-4824
email:sorachai.nitayapan@thai.amedd.army.mil

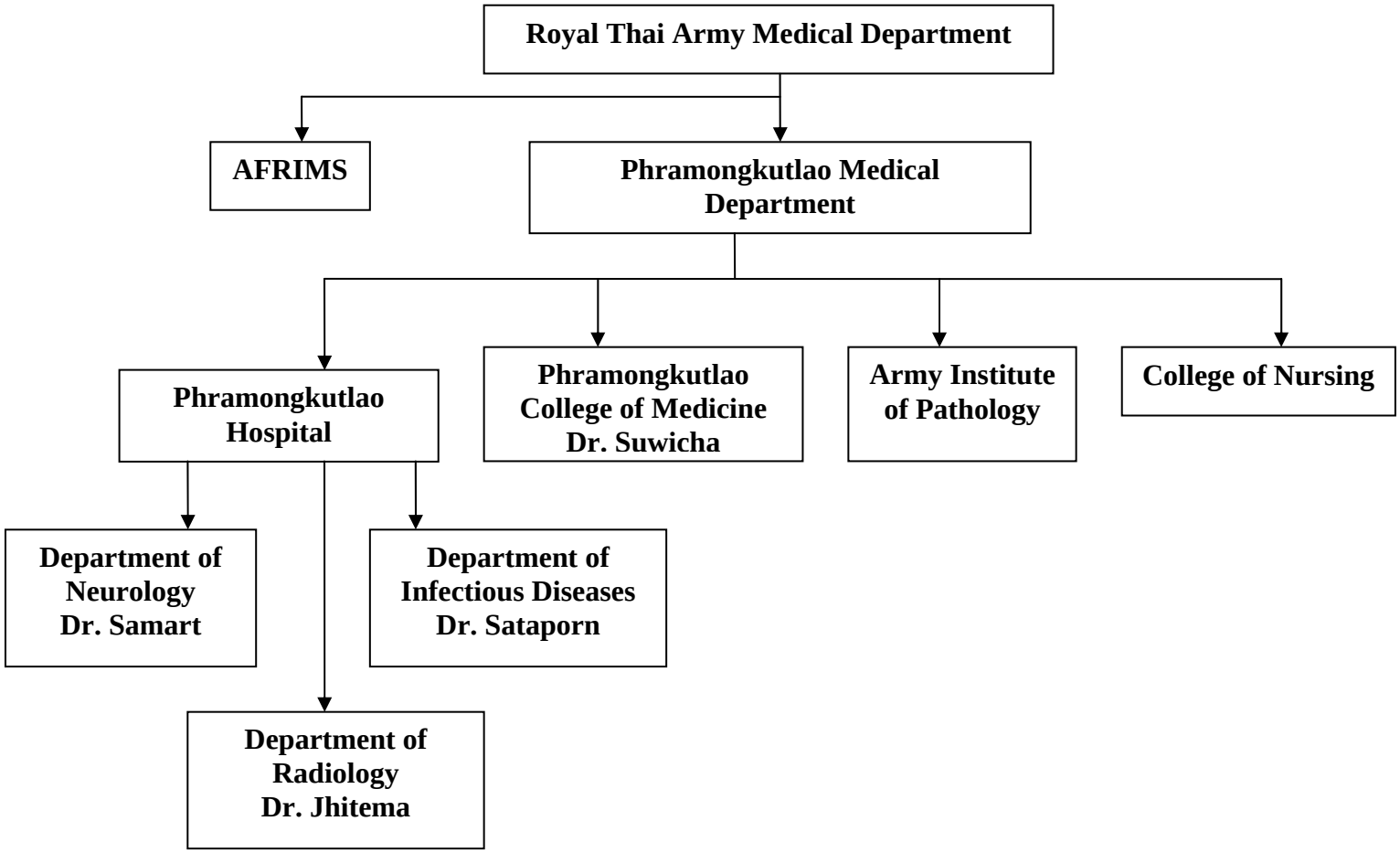
Thippawan Chuenchitra PhD (Col)
Chief, Department of Microbiology
Division of Research, AFRRIMS
315/6 Rajvithi Rd., Rajthevee
Bangkok 10400, Thailand
Phone: (662) 354-7861-69 ext. 2125
Fax: (662) 354-7854
Email: Thippawanc@afrims.org

Suchitra Sukwit B.Sc., MS
Chief, Division of Pathology,
Division of Research
AFRIMS
315/6 Rajvithi Rd., Rajthevee
Bangkok, 10400, Thailand
Phone: 66-01-826-6234
Email: 8266435@hellokitty.com

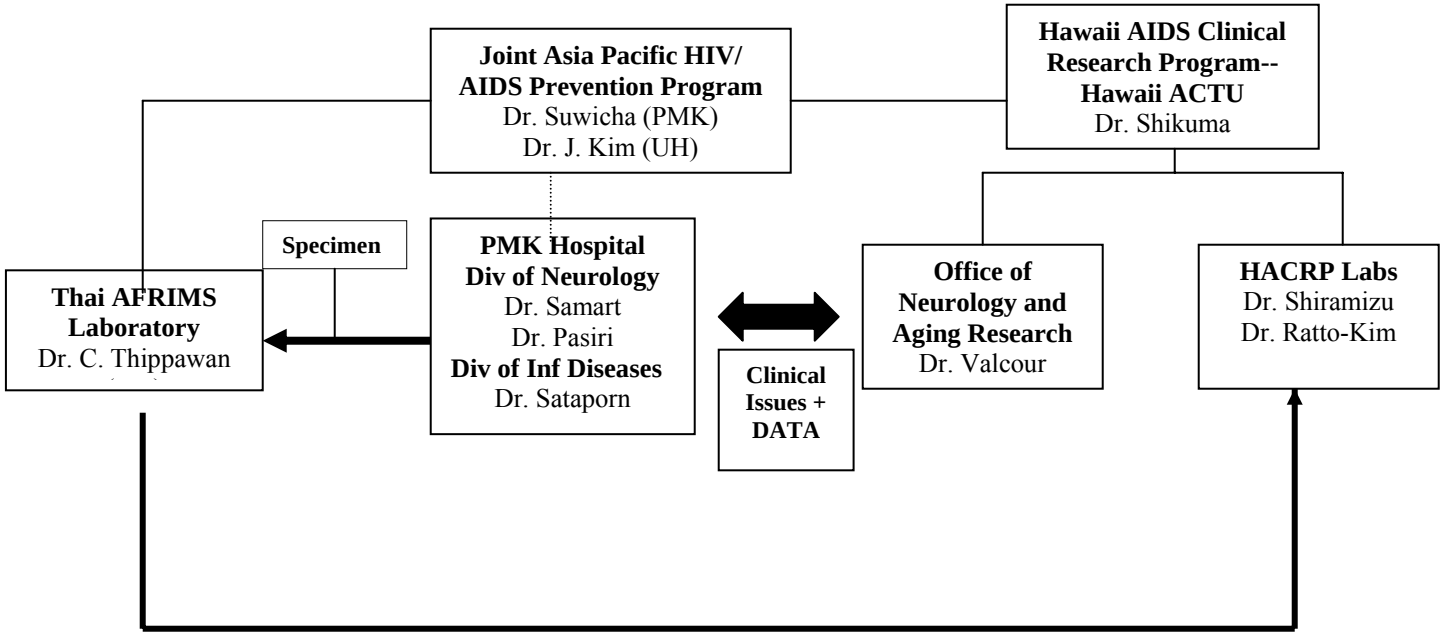
University of Hawaii Administrative Structure for Project



Phramongkutklao Medical Center Administrative Structure for Project



Schematic Diagram of Data and Specimen Flow for Project



RESEARCH PROPOSAL

This is a proposal to obtain pilot data and to assess logistical feasibility for intended Hawaii-Thailand joint NIH Exploratory/Developmental Research proposal on the research topic of HIV-associated dementia (HAD).

The proposal is written to include follow-up visits and evaluations to 24 months. The current budget only contains the initial baseline costs of this study. Application for additional funding to support the follow-up visits is planned.

Specific Aims

Main scientific aims:

1. To assess the relationship between monocyte/macrophage activation and dementia in ARV naïve patients living in Thailand.
    a. Assess presence of circulating activated macrophage phenotype using 4-color flow cytometry
    b. Assess cytokine production through ELISA assays of key cytokine products
    c. Explore other possible secretory products through proteonomics-based technology
2. To assess the relationship among proviral DNA levels, blood HIV viral load, CSF HIV viral load, and cognitive status among ARV naïve pateints with and without HIV dementia
3. To identify predictors of neurocogntive decline and survival at time of neurological consultation including relationship between MRI qualitative readings, findings on neurological examination, laboratory findings.

Main developmental aims

1. To extend our knowledge of the pathophysiologic mechanisms underlying the development of HIV-related dementia (HAD) in ARV naïve patients by developing a collaborative University of Hawaii-Phramongkutklao Medical Center research initiative.
2. To fully develop research infrastructure needed to support further HIV/AIDS collaborative research
    a. Develop reliable research-based neurocognitive and neurological characterization of HIV/AIDS patients using internationally validated measures.
    b. Further develop research core clinical team support to include nurses, research assistants, and physicians
    c. Maintain current high quality laboratory infrastructure and expand capabilities as needed and appropriate
    d. Fully assess laboratory specimen shipping capabilities to all key University of Hawaii research collaborators.

Background and Rationale:

HIV-associated Dementia contributes to the morbidity of HIV infection. Before the widespread use of combination HIV anti-retroviral (ARV) therapy in the United States, up to 15% of individuals with AIDS developed HAD and an additional 15% experienced HIV-related Minor Cognitive Motor Disorder (MC/MD), a milder form of cognitive and motor abnormality (1, 2).

Over the past decade, the epidemiology of HIV/AIDS has changed in the United States and in other countries where there is widespread use of ARV medications (3, 4). A substantial decline in the reported incidence of HAD has been found. However, the changes in prevalence have not been as apparent, possibly due to an improvement in life expectancy associated with common ARV medications use (5). There has also been an increased incidence of MCMD relative to HAD. Additionally, the proportion of individuals with HAD and a CD4 count greater than 200cells/mm^3 has increased. At autopsy, histopathologic evidence of HIV encephalopathy continues to be present in 25% of patients who succumb to AIDS - a rate that has not changed since widespread use of ARV (6). Taken together, these data suggest that cognitive dysfunction continues to be an important source of morbidity in HIV infection and may now be associated with less severe stages of disease.

There is growing concern that the currently seen cognitive decline in the United States' HIV population may not truly represent the classic form of HIV-related encephalopathy induced by pathophysiologic events set in motion by HIV (7, 8). Instead, it may represent a homogenous set of mechanisms to include factors associated with chronic disease, including chronic immune activation and chronic exposure to ARV (9). These changes significantly hinder the ability to identify HIV-specific pathogenic mechanisms and identification of specific areas for intervention strategies. Moreover, new technologies currently available in the United States, including proteomics technology, have not been utilized well in ARV naïve individuals, augmenting the potential for identification of novel HIV-specific neurocognitive correlates (10).

The University of Hawaii has developed notable experience in HIV-related neurocognitive disorders through NINDS (NIH) funded initiatives and multiple US-national collaborations. Specific identified strengths include the assessment of metabolic and immunological factors associated with neurocognitive outcomes, and clinical expertise in aging with HIV infection (11-13). Through national collaborations, we have developed the ability to apply proteomics and identify novel protein markers for neurocognitive outcomes. We have an approximately 250 patient cohort with excellent neurocognitive and neurological characterization with intent to expand to 400 (the *Hawaii Aging with HIV Cohort*; PI: Victor Valcour M.D.) We intend to extend this clinical research expertise to our partners in Bangkok, thus establishing a state-of-the-art HIV neurological research clinic in the heart of the Asia Pacific Region.

Rationale for Collaboration: In attempting to elucidate the pathophysiologic mechanisms underlying the development of HAD, it is currently difficult, in our Hawaii cohort and at other centers in the United States, to isolate the direct and inflammatory effects of the virus leading to the development of dementia because of the confounding variables of antiretroviral treatment, adverse experiences associated with ARV, and variation in duration of HIV illness. It is proposed that a complementary cohort of subjects who are naïve to anti-retroviral therapy at entry and who are without a history of substance abuse be established in Thailand. Comparative

studies between the Thailand and Hawaii cohorts may help to not only elucidate the pathophysiologic mechanisms underlying the development of HAD but also assist in delineating what non-viral confounding factors leading to dementia are impacting the HIV-infected population in Hawaii and the US. Simultaneously, we hope to develop research expertise needed for complicated HIV/AIDS protocols in Southeast Asia.

Great significance lies in the timing of this proposed effort. Thailand is planning to institute antiretroviral treatment as a standard of care for persons with advanced HIV infection, slated to begin in October of 2003. Individuals eligible for this intervention will include individuals with low CD4 t-lymphocyte counts, such as those with dementia in this proposed study. This is a milestone event for Thailand, representing a major breakthrough in HIV/AIDS care. We intend to utilize this opportunity to characterize a sample of this population before they initiate ARV and follow their course once ARV has been initiated. Further, there is little documentation of HIV dementia (or related disorders) in the medical literature within Thailand. This effort will assist Thai physicians and researchers in understanding the extent and unique characteristics of HIV-associated cognitive dysfunction in HIV-infected Thai nationals and provide data concerning the course of disease.

Our site investigators have active on-going research, some with collaborators at other U.S. universities, in the following areas that may be conducive to the construction of a hypothesis-driven proposal to the NIH:

1. Peripheral blood macrophage activation and HIV insertional mutagenesis [Bruce Shiramizu MD. (Hawaii)]
2. Role of CD4 cells in modulating macrophage activation [Silvia Ratto-Kim Ph.D. (Hawaii)]
3. Role of macrophage cytokine production in dementia [Hawaii site collaboration with Lynn Pulliam Ph.D. (University of California – San Francisco)]
4. Metabolic and mitochondrial dysfunction [Cecilia Shikuma M.D. and Mariana Gerschenson Ph.D. (Hawaii)]

In addition, the collaboration will utilize the Joint HIV/AIDS Regional Training Laboratory (JHARTL), which is a shared resource between Phramongkutklao Medical School and the Joint Asia-Pacific HIV/AIDS Prevention Program (University of Hawaii, the Center of Excellence in Disaster Management and Humanitarian Assistance, and Tripler Army Medical Center). JHARTL, through its technical capabilities and collaborations with the Thai Armed Forces Research Institute of Medical Sciences (AFRIMS), has access to CAP-certified HIV viral load assays and CD4/CD8 T cell counts.

Operational Methods:

1. Study Management and Key Personnel:

Study Management:

Clinical operations of the study will take place at Phramongkutklao Medical Center (PMK) Neurology and Infectious disease clinics. Individuals will be enrolled over a 12-month period of time for a comprehensive evaluation to include neurological examination (macro-neuro exam), neuropsychological testing (NP protocol *hotlink*), blood draw, MRI/MRS (HIV+ patients with dementia only) (MRI Protocol *hotlink*), and lumbar puncture (HIV+ patients with dementia only) (LP Protocol *hotlink*). The MRI/MRS and lumbar puncture will only be performed if medically indicated as determined by the PMK neurologist. The research nurse will conduct the clinical evaluations, excluding the neurological examination (which will be conducted by the MD) under the direction supervision of the PMK neurologist. Case report forms will be completed at the clinical site by the research nurse. Copies (without personal identifiers) will be sent by fax, express mail, or currier to the Office of Neurology and Aging Research at the University of Hawaii on a regular basis. Data entry and cleaning of data will be completed at the Hawaii site in consultation for clarification with PMK research nurse, as needed. All patient contact information will remain in Thailand; all specimens and data will be identified by unique alpha-numeric identifiers. No contact information nor identifying information will be available to the Hawaii site.

Blood and CSF specimens will be drawn by the research nurse at PMK. Standard laboratory testing will be performed by PMK. Other study specific bloods will be processed at the CAP certified research laboratory at the Armed Forces Research Institute of Medical Sciences following a specified protocol (Lab Processing Protocol *hotlink*).

Quality assurance for clinical aspects of the work and laboratory processing/storage will be directed by Dr. Valcour and Dr. Shiramizu, respectively. Face-to-face training will be provided for the research nurse. Training for neurologists will occur in person or by video teleconferencing (VTC). Quality assurance for neuropsychological testing will be provided by the PMK neuropsychologist on a bi-annual basis. A UH investigator or affiliate investigator trained and experienced in HIV neurological examinations will provide annual observation of one neurological examination annually. This will be completed in a face-to-face meeting whenever possible, or VTC if not possible.

Study Logistics:

The proposed funding would include partial support for a senior (Thailand) neurologist, Samart Nidhinandana MD, MSc, and junior (Thailand) neurologist, Pasiri Sithinamsuwan MD and an Infectious Disease specialist (Thailand), Sataporn Thitvichianlert MD. Clinic support staff is not requested as most work will be conducted by the research nurse. The participating physicians will complete recruitment of HIV+ individuals with the assistance of the research nurse. A full-time study nurse (RN) will be primarily responsible for the logistic operations of the study and for completion of the case report forms. The senior neurologist would provide project oversight

and technical guidance. The junior neurologist or licenced/certified designate (MD) would perform neurologic evaluations, lumbar puncture, and supervise clinical activities. The senior ID specialist will assist in the identification of appropriate non-demented HIV+ subjects. The nurse will assist in recruitment and follow-up, history taking, retrieval of data, completion of case report forms, and the administration of neuropsychologic testing (under the direction of a neuropsychologist, if deemed necessary). The University of Hawaii will provide the training needed to perform these duties. In addition, funds to support the laboratory testing, imaging (MRI/MRS), storage and shipping of specimens will be integrated into the proposal.

Victor Valcour M.D, University of Hawaii, will be primarily responsible for clinical research protocol development, clinical training and examination quality control. He will also be primarily responsible for data entry and manipulation. Cecilia Shikuma M.D, University of Hawaii, will be responsible for basic science research agenda as well as administrative and funding issues. Bruce Shiramizu M.D, University of Hawaii, will be responsible for specimen shipment and coordination, laboratory needs, and specimen quality assurance.

Timing of Visit and procedures:

1. Entry Study Visit should be done within 30 days of the Screening Study Visit
2. Entry MRI/MRS for HIV seropositive subjects with dementia should be done within 30 days before or after the Entry Study Visit
3. Entry Lumbar puncture for HIV seropositive subjects with dementia should be done within 30 days after the Entry Study Visit

2. Selection and recruitment
    a. Seropositive patients with dementia (n=15 subjects): Individuals for this arm of the study will consist of HIV+ individuals ≥ 20 years of age who are not currently receiving nor have ever received antiretroviral medications and who are suspected by the research neurologist to likely have neurocognitive deficits not explainable by opportunistic infections or causes other than HIV on the basis of clinical assesssment. Clinical assessment is anticipated to include the neurologist's assessment of patient's activities of daily living (ADL) and brief neurologic/ neuropsychologic evaluation to include the HIV dementia screen – international version. (Note: it is anticipated that these individuals will be eligible to receive ARV through standard of care practice in Thailand; this evaluation will immediately precced initiation of ARV in such cases. All efforts will be made to facilitate these referals).
    Exclusion criteria will include:
        i. Head injury with loss of consciousness greater than 1 hour
        ii. Current or past illicit drug use or positive drug screen for amphetamine, methamphetamines, cocaine, marijuana, or narcotics at either screening or entry.
        iii. Inability to provide informed consent or lack of designated surrogate who can provide consent
        iv. The following laboratory values:
            1. PT/PTT > the upper limit of normal (ULN) or INR > 1.1

2. Hemoglobin < 9.0 mg/dL
3. ALT > 5x ULN
4. serum Creatinine > 2x ULN

v. Acute illness within 30 days prior to entry, persistent and active AIDS-defining opportunistic infection or autoimmune disease. Stable treated opportunistic infections on maintenance therapy, minor infections such as oral thrush and Kaposi's Sarcoma limited to the skin will be allowed.
vi. Current or recent fevers or meningeal signs suggestive of CNS opportunistic infection.*
vii. History of pre-existing neurologic disease to include stroke, multiple sclerosis
viii. History of psychiatric illness including schizophrenia, bipolar disorder, anxiety disorder, panic attacks, or post traumatic stress disorder. Patients with active major depression will be excluded as well – patients with past depresion that is controled and patients with or minor depressive symptoms will be allowed to enroll.
ix. Known learning disability including dyslexia.
x. Positive Hepatitis C serology (Hepatitic C Ab)
xi. Confusion or other signs and symtoms of metabolic encephalopathy or delirium
xii. Mass consistent with opportunistic infection or tumor on CT or MRI of the head, or focal neurological deficit on examination consistent with possible brain lesion.*
xiii. Other conditions that could explain neurocognitive decline in the opinion of the investigator such as hypothyroidism, vitamin B12 deficiency or neurosyphilis.

* Patients diagnosed with opportunistic infection after CSF examination will be excluded from further analysis. In such a situation, an additional patient will be enrolled, as finances allow, to total 15 patients eligible for analysis.

b. Seropositive patients without dementia (n = 15 subjects): Each patient with dementia will be matched with a seropositive patient with similar age (same decade), education (less than high school degree, high school degree +/- some college, college degree +), gender, and CD4 group (<200 cells/mm^3, 200-350, 350+). These patients will be selected from the infectious disease clinic among patients who are HIV positive and are not currently receiving nor have ever received antiretroviral medications. (Note: Baseline evaluations will be completed before intiation of ARV in individuals planning to start ARV through standard of care practice in Thailand).
Exclusion criteria will include:

i. Significant complaints of memory or thinking problems. Mild forgetfulness that could be seen in HIV negative populations would be allowed.
ii. Head injury with loss of consciousness greater than 1 hour
iii. Current or past illicit drug use or positive drug screen for amphetamine, methamphetamines, cocaine, marajuana, or narcotics at either screening or entry.

iv. Inability to provide informed consent or lack of designated surrogate who can provide consent
v. The following laboratory values:
    1. PT/PTT > the upper limit of normal (ULN) or INR > 1.1
    2. Hemoglobin < 9.0 mg/dL
    3. ALT > 5x ULN
    4. serum Creatinine > 2x ULN
vi. Acute illness within 30 days prior to entry, persistent and active AIDS-defining opportunistic infection or autoimmune disease. Stable treated opportunistic infections on maintenance therapy, minor infections such as oral thrush and Kaposi's Sarcoma limited to the skin will be allowed.
vii. Current or recent fevers or meningeal signs suggestive of CNS opportunistic infection.*
viii. History of pre-existing neurologic disease to include stroke, multiple sclerosis
ix. History of psychiatric illness including schizophrenia, bipolar disorder, anxiety disorder, panic attacks, or post traumatic stress disorder. Patients with active major depression will be excluded as well – patients with past depresion that is controled and patients with or minor depressive symptoms will be allowed to enroll.
x. Known learning disability including dyslexia.
xi. Positive Hepatitis C serology (Hepatitic C Ab)
xii. Confusion or other signs and symtoms of metabolic encephalopathy or delirium
xiii. Mass consistent with opportunistic infection or tumor on CT or MRI of the head, or focal neurological deficit on examination consistent with possible brain lesion.*

* Patients diagnosed with opportunistic infection after CSF examination will be excluded from further analysis. In such a situation, an additional patient will be enrolled, as finances allow, to total 15 patients eligible for analysis.

c. Seronegative patients (n = 15 subjects): Each seropositive patient with dementia will be matched with a seronegative patient by age (same decade), and education (less than high school degree, high school degree +/- some college, college degree+), and gender. **Exclusion criteria will include:**

    i. Head injury with loss of consciousness greater than 1 hour
    ii. Current or past illicit drug use or positive drug screen for amphetamine, methamphetamines, cocaine, marajuana, or narcotics at either screening or entry.
    iii. Inability to provide informed consent or lack of designated surrogate who can provide consent
    iv. The following laboratory values:
        1. PT/PTT > the upper limit of normal (ULN) or INR > 1.1
        2. Hemoglobin < 9.0 mg/dL
        3. ALT > 5x ULN

4. serum Creatinine > 2x ULN

v. Acute illness within 30 days prior to entry, persistent and acute opportunistic infection or autoimmune disease.
vi. Current or recent fevers or meningeal signs suggestive of CNS opportunistic infection.
vii. History of pre-existing neurologic disease to include stroke, multiple sclerosis or autoimmune disease.
viii. History of psychiatric illness including schizophrenia, bipolar disorder, anxiety disorder, panic attacks, or post traumatic stress disorder. Patients with active major depression will be excluded as well – patients with past depresion that is controled and patients with or minor depressive symptoms will be allowed to enroll.
ix. Known learning disability including dyslexia
x. Positive Hepatitis C serology (Hepatitic C Ab)
xi. Confusion or other signs and symptoms of metabolic encephalopathy or delirium
xii. Focal neurological deficit on examination

3. Subject Evaluations Schema – baseline evaluations:
   a. Baseline demographics: DOB, gender, ethnicity, education, risk factor profile
   b. Assessment of function including activity of daily living questionnaire
   c. History of medical illnesses, medication history
   d. Neurological examination: All patients will have a neurological evaluation and neuropsychological evaluation to characterize neurocognitive and neurological status. (It is possible that patients within the non-dementia group will meet criteria for dementia after close testing is completed). Examination will include:
      i. AACTG macroneurological examination with emphasis on motor slowing, extrapyrimidal signs, CNS signs. (30- 40 minutes) (14, 15)
      ii. Karnofsky functional assessment
   e. Neuropsychological assessment:
      i. Clinical dementia rating scale;
      ii. HIV dementia screen
      iii. WHO/NIMH/UCLA International Battery (16), including:
         1. Timed gait (Motor speed/ fine motor control)
         2. Finger tapping (Motor speed/ fine motor control)
         3. Color trails 1 and 2 (Motor speed/ fine motor control, sustained attention, selective attention, cognitive flexibility)
         4. EIWA Block Design (Motor speed/ fine motor control)
         5. EIWA Digit Symbol (Motor speed/ fine motor control)
         6. Grooved Pegboard (Motor speed/ fine motor control)
         7. Trail Making A (Motor speed/ fine motor control, sustained attention)
         8. EIWA Digit Symbol (selective attention, cognitive flexibility)
         9. EIWA Block Design (perceptual motor analysis)
         10. WHO/UCLA Auditory Verbal Learning Test (verbal memory)
         11. Breif Visual Memory Retention Test- Revised (visual memory)
         12. Verbal Fluency – animals and first names (verbal fluency)

f. Thai Depression Inventory (17).
g. Contrast MRI of the brain with qualitative MRI reading/ MRS for HIV+ patients with dementia (MRI Protocol*hotlink*)
h. Final outcome assessment based on all available data (determined by neurologist in consultation with the PMK neuropsychologist.). If possible, it is intended that these diagnoses will be determined through monthly VTC conference calls with UH investigators. This consesnus conference will include the PMK neurologist(s), the PMK neuropsychologist, the UH neurologist, the UH neuropsychologist and the principal investigator Hawaii site (Dr. Valcour):
    i. Diagnosis based on 1991 American Academy of Neurology (AAN Criteria*hotlink*) (1)criteria as:
        1. No impairment
        2. Neuropsychological abnormal; does not meet MCMD or dementia criteria
        3. Minor Cognitive Motor Disorder (MCMD)
        4. HIV-associated Dementia (HAD)
    ii. Staging based on Memorial Sloan Kettering scale
        0 = normal
        0.5 = equivocal abnormalities
        1 = mild dementia
        2 = moderate dementia
        3 = severe dementia
        4 = end-stage disease

4. Subject evaluations, longitudinal:
    a. All seropositive subjects will have the neuropsychological battery and neurological examination repeated every 6 months, in funding available. Re-assessment of neurocognitive outcomes will be determined as well.

5. Blood, urine and CSF specimens (summarized in Laboratory Processing Chart, Appendix III)

Note: Bloodwork labeled FASTING can be done together or separate from other entry bloodwork as long as the patient is FASTING. If neuropsychological evaluatiion is planned after fasting bloodwork is done, the patient MUST be fed prior to the performance of the neuropsychological evaluation. (**Fasting is defined** as nothing by mouth except water and meds for >12 hrs

a. HIV Seropositive Patients WITH Dementia)

i. Screening Labs

Blood (Total 29 mL):

1. Purple top EDTA tube:
   One 3 mL tube (CBC)
2. Tiger top SST tubes:
   One 5 mL tube (Chem)
   Five 3 mL tubes (Hepatitis C, TSH/free T4, Cryptococcal

antigen, VDRL/FTA-abs, B12)

3. Gray top NaF/K oxalate tube:
   One 3 mL tube (glucose)
4. Blue top sodium citrate tube:
   One 3 mL tube (PT/PTT)

Urine:

5. Urine for toxicology screen

ii. Entry Labs:

Blood (Total 65 mL):

1. Purple top EDTA tube:
   One 3 mL tube (CBC & CD4/CD8)
   One 3 mL tube (HIV RNA) [MUST be done on day of and ideally at time of lumbar puncture]
   One 7 mL tube (FASTING plasma and PBMC [in DSMO] Repository)
2. Green top heparin tubes:
   One 5 mL tube (advanced flow)
   Three 7 mL tubes (macrophage isolation and supernatants)
   One 7 mL tube (FASTING plasma and PBMC [in DSMO] repository)
3. Tiger top SST tubes:
   Two 7 mL tubes (FASTING serum repository)
4. Gray top NaF/K oxalate tube:
   One 5 mL tube (FASTING glucose repository)

Urine

5. Urine for toxicology screen
6. Urine (10-20 ml) for Urine repository

CSF

CSF will be drawn in 4 tubes in order from 1 to 4 as follows:

a. **Tube # 1**: 1 cc to be sent for protein, glucose, VDRL, CryptococcusCryptococus Ag. (1.5 mL)
b. **Tube # 2**: 4 cc to be stored (repository)
c. **Tube # 3**: 1 cc to be sent for cell count
d. **Tube # 4**: 4 cc to be stored (repository and VL)

Note: Matching blood as above for HIV RNA MUST be drawn at the time of lumbar puncture.

iii. Yearly Labs:

Blood (Total 70 mL):

1. Tiger top SST tubes:
   One 5 mL tube (Chem)
   Two 7 mL tubes (FASTING serum repository)
2. Purple top EDTA tube:
   One 3 mL tube (CBC & CD4/CD8)

One 3 mL tube (HIV RNA)
One 7 mL tube (FASTING plasma and PBMC [in DSMO] Repository)

3. Green top heparin tubes:
   One 5 mL tube (advanced flow)
   Three 7 mL tubes (macrophage isolation and supernatants)
   One 7 mL tube (FASTING plasma and PBMC [in DSMO] repository)
4. Gray top NaF/K oxalate tube:
   One 5 mL tube (FASTING glucose repository)

Urine

5. Urine for toxicology screen
6. Urine (10-20 ml) for Urine repository

b. HIV Seropositive Patients WITHOUT Dementia)

i. Screening Labs

Blood (Total 20 mL):

1. Purple top EDTA tube:
   One 3 mL tube (CBC & CD4/CD8)
2. Tiger top SST tubes:
   One 5 mL tube (Chem)
   Two 3 mL tubes (Hepatitis C, Cryptococcal antigen)
3. Gray top NaF/K oxalate tube:
   One 3 mL tube (glucose)
4. Blue top sodium citrate tube:
   One 3 mL tube (PT/PTT)

Urine:

5. Urine for toxicology screen

ii. Entry Labs

Blood (Total 62 mL)

1. Purple top EDTA tube:
   One 3 mL tube (HIV RNA) .
   One 7 mL tube (FASTING plasma and PBMC [in DSMO] Repository)
2. Green top heparin tubes:
   One 5 mL tube (advanced flow)
   Three 7 mL tubes (macrophage isolation and supernatants)
   One 7 mL tube (FASTING plasma and PBMC [in DSMO] repository)
3. Tiger top SST tubes:
   Two 7 mL tubes (FASTING serum repository)
4. Gray top NaF/K oxalate tube:
   One 5 mL tube (FASTING glucose repository)

Urine

5. Urine for toxicology screen
6. Urine (10-20 ml) for Urine repository

iii. Yearly Labs

Blood (Total 70 mL):

1. Tiger top SST tubes:
   One 5 mL tube (Chem)
   Two 7 mL tubes (FASTING serum repository)
2. Purple top EDTA tube:
   One 3 mL tube (CBC & CD4/CD8)
   One 3 mL tube (HIV RNA)
   One 7 mL tube (FASTING plasma and PBMC [in DSMO] repository)
3. Green top heparin tubes:
   One 5 mL tube (advanced flow)
   Three 7 mL tubes (macrophage isolation and supernatants)
   One 7 mL tube (FASTING plasma and PBMC [in DSMO] repository)
4. Gray top NaF/K oxalate tube:
   One 5 mL tube (FASTING glucose repository)

Urine

5. Urine for toxicology screen
6. Urine (10-20 ml) for Urine repository

c. **HIV Seronegative Patient:**

i. Screening Labs

Blood (Total 11 mL):

1. Tiger top SST tubes:
   One 5 mL tube (Chem)
   Two 3 mL tubes (Hepatitis C, HIV ELISA with confirmatory Western Blot)

Urine

Urine for Toxicology Screen

ii. Entry Labs

Bloods (Total 62 mL)

1. Purple top EDTA tube:
   One 3 mL tube (CBC & CD4/CD8)
   One 7 mL tube (FASTING plasma and PBMC [in DSMO])
2. Tiger top SST tubes:
   Two 7 mL tubes (FASTING serum repository)
3. Green top heparin tubes:
   One 5 mL tube (advanced flow)
   Three 7 mL tubes (macrophage isolation and supernatants)
   One 7 mL tube (FASTING plasma and PBMC [in DSMO] repository)

4. Gray top NaF/K oxalate tube:
   One 3 mL tube (FASTING glucose repository)

Urine

1. Urine for toxicology screen
2. Urine (10-20 mL) for repository

Table: Schema of Evaluations

Evaluations in HIV seropositive subjects (with dementia):

		Screening	Entry	6 months	12 months	18 months	24 months
Inclusion/exclusion form		**X**					
Baseline demographics		**X**					
Neurological Examination		**X**		**X**	**X**	**X**	**X**
Neuropsychological evaluation			**X**	**X**	**X**	**X**	**X**
Lumbar Puncture (LP)			**X**[a]				
MRI with contrast enhancement			**X**[a]				
Interim evaluation form				**X**	**X**	**X**	**X**
Laboratory/Specimens							
	CBC (PMK)	**X (3mL)**					**X**
	Chemistries (PMK)[b]	**X (5mL)**			**X (5mL)**		**X (5mL)**
	Glucose (PMK)	**X (3mL)**					
	PT/PTT (PMK)	**X (3mL)**					
	HCV Serology (PMK)	**X (3mL)**					
	TSH/free T4	**X (3mL)**					
	Serum Cryptococcal Antigen	**X (3mL)**					
	VDRL/FTA-abs	**X (3mL)**					
	B12 Level	**X (3mL)**					
	Urine Toxicology Screen (AFRIMS)	**X**	**X**		**X**		**X**
	Urine for repository (AFRIMS)		**X**		**X**		**X**
	HIV Viral Load (AFRIMS)		**X**[c] **(3mL)**		**X (3mL)**		**X (3mL)**
	CD4/CD8 counts & CBC/Diff (AFRIMS)		**X (3mL)**		**X (3mL)**		**X (3mL)**
	Advanced Flow (AFRIMS)		**X (5mL)**		**X (5mL)**		**X (5mL)**
	FASTING plasma and PBMC repository [EDTA] (AFRIMS)		**X (7mL)**		**X (7mL)**		**X (7mL)**
	FASTING plasma and PBMC repository [heparin] (AFRIMS)		**X (7mL)**		**X (7mL)**		**X (7mL)**
	Blood for macrophage isolation and supernatants (AFRIMS)		**X (21mL)**		**X (21mL)**		**X (21mL)**
	Blood for FASTING serum repository (AFRIMS)		**X (14mL)**		**X (14mL)**		**X (14mL)**
	Blood for FASTING glucose repository (AFRIMS)[d]		**X (5mL)**		**X (5mL)**		**X (5mL)**
	CSF cell count, glucose and protein (PMK)		**X**				
	CSF viral load and repository (AFRIMS)		**X**				
	Total volume of blood	**29 mL**	**65 mL**		**70 mL**		**70 mL**

Evaluations in HIV seropositive subjects (without dementia):

		Screening	Entry	6 months	12 months	18 months	24 months
Inclusion/exclusion form		**X**					
Baseline demographics		**X**					
Neurological Examination		**X**		**X**	**X**	**X**	**X**
Neuropsychological evaluation			**X**	**X**	**X**	**X**	**X**
Interim evaluation form				**X**	**X**	**X**	**X**
Laboratory/Specimens							
	CBC & CD4/CD8 count (AFRIMS)	**X (3mL)**			**X (3ml)**		**X (3mL)**
	Chemistries (PMK)[a]	**X (5mL)**			**X (5mL)**		**X (5mL)**
	Glucose (PMK)	**X (3mL)**					
	PT/PTT (PMK)	**X (3mL)**					
	HCV Serology (PMK)	**X (3mL)**					
	Serum Cryptococcal Antigen	**X (3mL)**					
	Urine Toxicology Screen (AFRIMS)	**X**	**X**		**X**		**X**
	Urine for repository (AFRIMS)		**X**		**X**		**X**
	HIV Viral Load (AFRIMS) (Same day as LP)		**X (3mL)**		**X (3mL)**		**X (3mL)**
	Advanced Flow (AFRIMS)		**X (5mL)**		**X (5mL)**		**X (5mL)**
	FASTING plasma and PBMC repository [EDTA](AFRIMS)		**X (7mL)**		**X (7mL)**		**X (7mL)**
	FASTING plasma and PBMC repository [heparin] (AFRIMS)		**X (7mL)**		**X (7mL)**		**X (7mL)**
	Blood for macrophage isolation and supernatants (AFRIMS)		**X (21mL)**		**X (21mL)**		**X (21mL)**
	Blood for FASTING serum repository (AFRIMS)		**X (14mL)**		**X (14mL)**		**X (14mL)**
	Blood for FASTING glucose repository (AFRIMS)[b]		**X (5mL)**		**X (5mL)**		**X (5mL)**
	Total volume of blood	**20 mL**	**62 mL**		**70 mL**		**70 mL**

a. To be done within 30 days before or after entry visit
b. Cholesterol, Triglycerides, T Bili, Alk Phos, ALT, Creatinine
c. To be done at the time of lumbar puncture
d. In NaF/K oxalate (gray-top) tube

Evaluations in HIV seronegative subjects:

		Screening/ Entry	
Inclusion/exclusion form		**X**	
Baseline demographics		**X**	
Neurological Examination		**X**	
Neuropsychological evaluation			**X**
Laboratory/Specimens			
	Chemistries (PMK)[a]	**X (5mL)**	
	HIV ELISA with confirmatory Western Blot (PMK)	**X (3mL)**	
	HCV Serology (PMK)	**X (3mL)**	
	Urine Tox icology Screen (AFRIMS)	**X**	**X**
	Urine for repository (AFRIMS)		**X**
	CD4/CD8 & CBC with Diff (AFRIMS)		**X (3mL)**
	Advanced Flow (AFRIMS)		**X (5mL)**
	FASTING plasma and PBMC Repository [EDTA] (AFRIMS)		**X (7mL)**
	FASTING plasma and PBMC repository [heparin] (AFRIMS)		**X (7mL)**
	Blood for macrophage isolation and supernatants (AFRIMS)		**X (21mL)**
	Blood for FASTING serum repository (AFRIMS)		**X (14mL)**
	Blood for FASTING glucose repository (AFRIMS)[b]		**X (5mL)**
	Total volume of blood	**11 mL**	**62 mL**

a. Cholesterol, Triglycerides, T Bili, Alk Phos, ALT, Creatinine

b. In NaF/K oxalate (gray-top) tube

Lumbar Puncture Protocol

The Research nurse greets the participant and calls the physician. The participant will be given the consent to read, but the physician will consent the participant directly after explaining the procedure. The Research nurse will make sure that appropriate laboratory results are available (PT/PTT, hematocrit, and platelet counts) and that the MRI reading is available. The physician will ensure that there are no contra-indications to LP, to include findings on MRI which should be completed before lumbar puncture.

The research nurse then takes and records the participant's vital signs and assists the physician with the LP.

After the LP, participants will lie prone for 10 minutes, then remain supine in any position that is comfortable for another 50 minutes and will be encouraged to drink oral fluids (water, juice) over the next 50 minutes. The physician or nurse will take their vital signs, check the LP site, ensure that the participant is fine, and discharge them. All information is recorded and signed. The physician has final signoff on the form. The research nurse will make a follow-up phone call to the participant 24 – 72 hours after the LP to evaluate for side effects and involve the research physician in management of any untoward effects.

Statistical Concerns:

The primary aim of this pilot project is to develop a strong functioning University of Hawaii-Phramongkutlao Medical Center collaboration. This specifically involves developing research HIV/AIDS neurological and neuropsychological capabilities. Further, it involves ensuring full high-quality laboratory specimen acquisition, processing and shipping capabilities to the University of Hawaii and all applicable collaborators on the continental United States. The long-term goal is to provide concrete resource and facilities information necessary for a successful NIH-funded r21 grant application, which in turn will be designed to acquire pilot data for larger analyses. (see appendix 6 for further details of the statistical section)

Several aspects of the data acquired will, however be utilized for hypothesis generating, specifically proteomics technology. Because this effort encompasses facility and resource building goals and hypothesis generating aims, sample calculations are not included.

(Note: Full statistical section for NIH application to complete longitudinal component of this project is attached as appendix VI)

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Appendix I

Brain MRI Protocol for UH-PMK001 with optional MRS component

This protocol is currently in use at PMK for clinical use. The MRS series will be added, if available (optional)

Software version 5.8.

Series 1: T1-weighted Sagital

Sagital, 2D Spin Echo, TE 8ms, TR 360ms, 5mm slice thickness with 2.0mm slice separation, FOV 22cm

Series 2: FSE-XL/90

Axial, TE 84.5ms, TR 3200ms, FOV 20cm, 5mm slice thickness with 2.0mm slice separation, 3nex

Series 3: Flair/90

Axial, TE 165ms, TR 11002ms, 32KHz Bandwidth, T1 2200ms, 5mm slice thickness with 2.0mm slice separation, 2nex

Series 4: T1-weighted Axial

Axial, 2D Spin Echo, TE 8ms, TR 360ms, 5mm slice thickness with 2.0mm slice separation

Series 5: Gradient Echo/25

Coronal, TE 20ms, TR 540ms, FOV 20cm, 5mm slice thickness with 2.0mm slice separation, 2nex

Series 6: MRS- probe-p (optional – based on availablitly)

Axial, Spectro, SE, EDR, GXROI (prescribed image from series 4, frontal-white matter), probe-p (type-in), TE=35ms. TR=3000ms, Voxel size 20x20x15mm (thickness = 15mm), opuser3 = 1, opuser4 = 128, opnex=8

Series 7: MRS - basal ganglia (optional – based on availability)

Completed as described in series 6 except voxel location is at the basal ganglia

Total acquisition time: ca. 40 min (series1-5 = 25min, series6-7=15min).

Appendix II: The 1991 AAN criteria (taken from Neurology 1991):

Clinical Diagnosis	NP and Neuro criteria	Comments/Characteristics
Normal	• **Neuropsychologically and neurologically within normal limits**	• Normal mental and motor function, typically minimal signs of disease.
NP abnormal	• **Mild neuropsychological or neurological findings, insufficient to meet criteria for MCMD or dementia**	• Minimal signs of disease
MCMD	• All stages in this category must meet MCMD criteria which includes functional complaints. **For MCMD - Specifically must have:** *Probable*: Must have EACH of the following: 1. Cognitive/motor/behavioral abnormality. Must have BOTH: a. At least 2 of the following symptoms present for at least 1 month by patient report or informant: i. Impaired attention of concentration ii. Mental slowing iii. Impaired memory iv. Slowed movements v. Incoordination vi. Personality change or irritability or emotional lability AND b. Acquired cognitive/motor abnormality on exam or testing. Examples include: i. Fine motor speed ii. Manual dexterity iii. Perceptual motor skills iv. Attention/concentration v. Speed of processing of information vi. Abstraction/reasoning vii. Visuospatial skills viii. Memory/learning ix. Speech/language 2. Does not meet criteria for dementia 3. No other potential etiology to the findings in 1 and 2. ***Possible: Must meet 1-2 of the criteria above, but either:*** 1. Another potential etiology exists or 2. Clinical evaluation is incomplete.	- Mild abnormalities in function, typically not affecting ADLs or IADLs. Typically able to complete all but more demanding aspects of daily life

Dementia	• All stages must meet HAD criteria which requires functional level greater than 0 **For HAD - Specifically must have:** *Probable*: Must have each of the following: 1. Acquired abnormality in at least 2 of the following cognitive abilities, present for at least 1 month: a. Attention/concentration b. Speed of processing information c. Abstraction/reasoning d. Visuospatial skills e. Memory/learning f. Speech/language 2. At least one of the following a. Acquired abnormality in motor function or performance. Examples: i. Slowed rapid movements ii. Abnormal gait iii. Limb incoordination iv. Hyperreflexia v. Hypertonia vi. Weakness vii. Fine motor speed viii. Manual dexterity ix. Perceptual motor skills b. Declined in motivational or emotional control or change in social behavior. Examples include i. Change in personality ii. Apathy iii. Inertia iv. Irritability v. Emotional lability vi. Impaired judgment characterized by socially inappropriate behavior or disinhibition 3. Absence of clouding of consciousness 4. No other potential etiology to the findings in 1-3. ***Possible: Must meet 1-3 of the criteria above, but either:*** 1. Another potential etiology exists or 2. Clinical evaluation is incomplete.	-stage 1,2,3,4 by MSK

APPENDIX III. AFRIMS LABORATORY PROCESSING CHART

Protocol # UHTHAI 001 Updated: 06/10/04

Contact: Bruce Shiramizu/Silvia Ratto-Kim/Pua Kondo Phone: (808) 737-2751 email: bshirami@hawaii.edu

Specimen Collection & Handling	Tests	Processing
Blood purple top EDTA tube	CBC/CD4/CD8 count	**Standard protocol**
Urine in urine collection cup	**Urine toxicology screen**	**Urine toxicology test as per manufacturer's instructions.**
Blood green top heparin tube Blood purple top EDTA tube	**FASTING** plasma/cells (in DMSO) repository	**Standard plasma/cells (DMSO) protocols; label w/specimen number, pid, protocol, vid, date of draw, primary (BLD), anticoagulant (HEP/EDT), derivative (PL2), additive (DMS), volume of aliquot. Ship regularly to: University of Hawaii.**
Blood tiger top SST tube Invert gently 10-15 times	**FASTING** serum repository	**Standard serum protocol; label similar to above. Ship regularly or on request to University of Hawaii.**
Blood grey top NaF/K oxalate (SPO) tube	**FASTING** glucose repository	Standard glucose protocol; label similar to above. Ship regularly or on request to University of Hawaii.
Blood green top heparin tube	Advanced flow markers (macrophages, others)	**See Appendix IV**
Blood green top heparin tubes	Macrophage isolation	See Appendix V
Urine in collection cup	**Urine repository**	**Standard urine repository protocol; label w/specimen number, pid, protocol, vid, date of draw, primary (URN), anticoagulant (NON), derivative (FLD or PEN), volume of aliquot. Ship regularly or on request to: University of Hawaii**
CSF; Process within 1 hour or as soon as possible	HIV viral load and repository	Standard protocol; label w/specimen number, pid, protocol, vid, date of draw, primary (CSF), anticoagulant (NON), derivative (FLD or CLN), additive for CLN only (DMS), volume of aliquot. Ship regularly or on request to: University of Hawaii
Blood 5 mL purple top EDTA tube; invert gently 10-15 times	HIV viral load (HIV-1 RNA/RT-PCR)	Plasma; process, store and batch as above.
Ship to: Hawaii AIDS Clinical Research Program Laboratory c/o Pua Kondo, 3675 Kilauea Ave., Young Bldg., Basement, Honolulu, Hawaii, USA 96816; phone: 808-737-2751		

APPENDIX IV

Percoll and Advanced Flow Cytometry

ISOLATION OF MONOCYTES USING PERCOLL GRADIENT FOR CELL SURFACE STAINING

I. PREPARATION

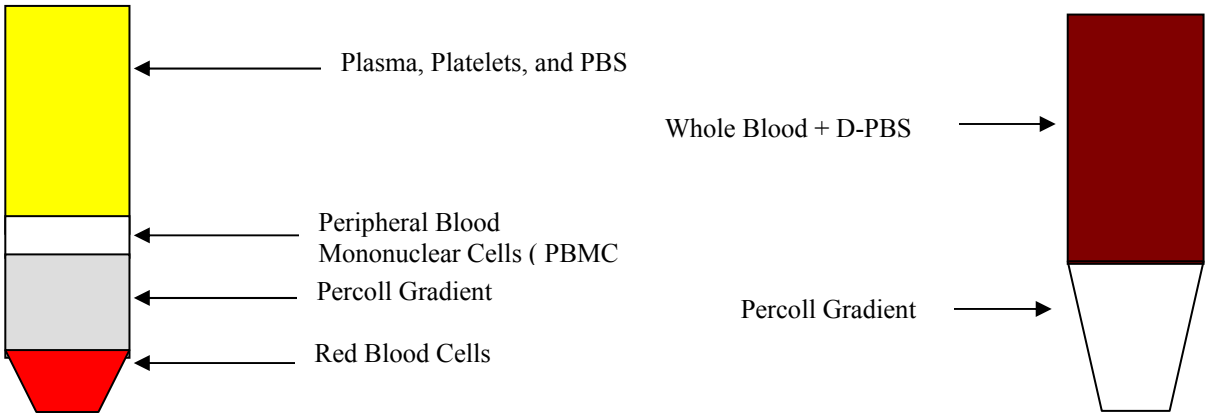
A. Reagents and Supplies

1. Whole Blood (heparin)
2. Percoll (ρ=1.087)
3. D-PBS w/out Ca&Mg
4. 15,50 ml conicles
5. Underpad
6. Stripette: 5,10,25,50 ml
7. 70% Ethanol
8. disposable gloves
9. Bleach

B. Instrumentation

1. Centrifuge
2. Pipetter
3. Pipet Dispenser
4. Hood

II. METHOD



1. Prepare Hood: sterilize with 70% Ethanol and place absorbent mat over area
2. Label 2x50ml conicles (1 with whole blood +DPBS; 1 with Percoll)
3. In the 50 ml conicle labeled whole blood + D-PBS make a 1:2 dilution with the whole blood and D-PBS; slowly mix
   (ex: 10ml of whole blood : 10ml of D-PBS)
4. In the 50 ml conicle labeled Percoll, depending on the volume of blood, add equal volume of Percoll Gradient
   (ex: 10ml of whole blood: 10ml of Percoll Gradient)
5. Overlay method: add the mixed whole blood + D-PBS onto the Percoll gently layering on top of percoll while maintaining the interface
6. Spin @ 2000RPM (800G) (25^{o}C) for 30 minutes with the **BREAK OFF!**
7. Collect the interface ring (PBMC) and place into a 50ml conicle using a 5mL stripette
8. Wash cells with D-PBS (bring to a volume of 50ml) and spin @ 1000-1200RPM (400G) with the break on for 10 minutes, decant & resuspend; Repeat wash
9. Resuspend cells to count or for use in Flow Cytometry

3-COLOR CELL SURFACE STAINING FOR FLOW

PREPARATION

Reagents and Supplies

Monoclonal Antibodies (see attached sheet)
12x4ml polystyrene falcon tubes
D-PBS w/out Ca & Mg
1% Paraformaldehyde (cell fixation)
Pipetter
10ul,100ul tips
Vortex
Low speed centrifuge

METHOD

STAINING AND FIXING CELLS

For each patient sample, label 12 falcon tubes accordingly:

Tube 1. G1/G2a/G2a
Tube 2. CD14 FITC
Tube 3. CD14 PE
Tube 4. 14/16/Anti-HLADR
Tube 5. 45/14/3
Tube 6. 14/45
Tube 7. 45RA/62L/CD8
Tube 8. 45RA/62L/CD4
Tube 9. 8/38/Anti-HLADR
Tube10. 4/38/Anti-HLADR
Tube11. LIN1/123/Anti-HLADR
Tube12. LIN1/11c/Anti-HLADR

Place 10ul of each monoclonal antibody stain into the tubes according to each label (CHANGE TIPS BETWEEN EACH STAIN!)
Resuspend cells isolated with Percoll gradient with 1.2ml of D-PBS
Add 100ul of cell suspension per tube
Vortex each sample @ low speed for 5 seconds
Incubate for 15-30 minutes @ room temperature
WRAP TUBES WITH FOIL TO KEEP LIGHT OUT!
Wash with 2ml of D-PBS per tube
Centrifuge @ 1200-1500 RPM (400G) for 10 minutes @ 25^{o}C
Decant and Resuspend in 500ul (1% Paraformaldeyde); vortex
Cover tubes with foil to keep light out and store @ 4^{o}C overnight for flow cytometric analysis

SNRP 005 3-COLOR STAINING PANEL

1	**MOUSE IgG1 FITC**	**11**	**CD38 PE**
2	**MOUSE IgG2a PE**	**12**	**CD4 FTIC**
3	**MOUSE IgG2a PERCP**	**13**	**CD8 FITC**
4	**CD14 FITC**	**14**	**CD3 PERCP**
5	**CD14 PE**	**15**	**CD4 PERCP**
6	**CD16 PE**	**16**	**CD8 PERCP**
7	**ANTI-HLA-DR PERCP**	**17**	**CD123 PE**
8	**CD45 PE**	**18**	**CD11C PE**
9	**CD45 RA FITC**	**19**	**CD62L PE**
10	**LIN1 FITC**		

APPENDIX V
Macrophage Enrichment and CD14 + Isolation by Magnetic Separation

Sterile Reagents:
10X saline (8.5% NaCl)
Ca^{2+} and Mg^{2+} free PBS
Percoll (Sigma P-1644)
RPMI-1640
Heat inactivated FBS
L-glutamine
Gentamycin

Blood:
Minimum 25 ml fresh blood
Collect in heparin tubes

Caution: HIV will be present in plasma and monocytes isolated from infected individuals.

Enrichment for monocytes by density gradient centrifugation with Percoll

1. Adjust Percoll density to 1.089 by diluting 25 ml Percoll with 11 ml ddsH_2O. Add 4 ml 10X saline to make solution isotonic. Chill solution to 4°C.
2. Dilute 25 ml blood 1:1 with cold PBS in 50 ml Falcon tube. Mix by inversion.
3. Prepare 2 x 50 ml Falcon tubes by adding 10–12 ml Percoll solution to each tube.
4. Gently layer 24-32 ml of diluted blood onto the Percoll solution maintaining the interface.
5. Centrifuge tubes at 600 x g in a swinging bucket rotor for 15 minutes at 4°C without brake. The Percoll gradient will spontaneously form and the monocytes will localize near the plasma/Percoll interface (cloudy band).
6. Remove top layer of plasma just above the Percoll interface with a sterile disposable Pasteur pipette. Clarify at high speed to remove cells and debris. Store at -70°C.
7. Retrieve monocytes (cloudy band) with a disposable sterile Pasteur pipette. Transfer cells to a 50 ml Falcon tube containing 40 ml cold PBS. Pellet cells at 300 x g for 15 min at 4°C. Carefully remove supernatant with a pipette.
8. Wash cells twice in PBS at 200 x g for 12 min at 4°C. At this speed, platelets should remain in solution.
9. Carefully remove supernatant and resuspend cells in cold PBS. Count cells on hemocytometer. Expect to isolate 1-10 x 10^7 cells. (Maximum number of cells that can be used with MiniMACS is 2 x 10^8 total cells/MS column.) Proceed to magnetic labeling of target monocytes.

Direct magnetic labeling of CD14 + cells with CD-14 MACS Microbeads (Miltenyi Biotec)

1. 20 µl of Microbeads will label up to 1 x 10^7 target monocytes.
2. Spin down cells and resuspend in fresh PBS. The final labeling volume should be 100 µl per 1 x 10^7 total cells. Therefore a pellet of 1 x 10^7 total cells is resuspended in 80 µl PBS and labeled with 20 µl CD-14 MACS Microbeads.
3. Mix well and incubate for 15-30 minutes at 4-8°C.
4. Wash cells by adding 10-20X labeling volume. Centrifuge at 300 x g for 10 min and carefully remove supernatant with a pipette. Resuspend cells in 500 µl PBS per 1 x 10^8 total cells and proceed to magnetic separation.

Magnetic separation of CD14 + cells with MiniMACS

1. Attach MiniMACS Separation Unit (magnet) to MACS MultiStand.
2. Place the MS column in the MiniMACS Separation Unit.
3. Rinse MS column by pipetting 500 µl cold PBS on top. Let the buffer flow through and discard the effluent. (Columns are flow stop and do not run dry.)
4. Apply magnetically labeled cells to the column and let the CD14 negative cells pass through the column. Collect effluent as the negative fraction. Pellet cells and store at – 70°C for genotyping.
5. Wash column with 3 x 500 µl cold PBS. (Always let the entire amount of buffer flow through the column before applying new buffer.) Collect total effluent as the negative fraction.
6. Remove MS column from the magnet and place in a sterile collection tube.
7. Apply 1 ml PBS onto the column and flush out the positive fraction by pipetting down the side of the column and using the plunger supplied with the column. Count cells with a hemocytometer by diluting 10 µl aliquot 10 fold. Expect to isolate 10% of the total cell isolated from the Percoll enrichment step.
8. Dilute cells to 1 x 10^5 cells/ml into RPMI-1640 supplemented with 10% FBS, 2 mM L-glutamine and 55.5 µg/ml gentamycin.

Culturing of CD14 + cells to generate conditioned media

1. Dilute 1 x 10^5 cells/ml into RPMI-1640 supplemented with 10% FBS, 2 mM L-glutamine and 55.5 µg/ml gentamycin.
2. Distribute 3 ml/well of a Falcon Multiwell Primaria 6-well culture plate #35-3864 (Becton Dickinson Labware, Franklin Lakes, NJ). **Note: If the number of CD14+ monocytes isolated is limited, plate only 2 wells**.
3. Incubate for 7 days at 37°C in 10% CO_2.
4. At the end of the culturing period, remove conditioned media and store at -70°C.

APPENDIX VI

Statistical Considerations and contingencies

Our primary endpoint for specific aim 1 (and the basis for the sample size calculations) will be the difference in percent monocyte activation at the completion of the study in individuals with HAD relative to individuals without HAD. The analysis will consist of a *t*-test between the means of these two groups. All tests of significance will be at an alpha of 0.05. Previous research (see Table 1) suggests that following HAART, the group of seropositive individuals with HAD will have a mean (± SEM) percent M/Mφ activation of approximately 30 ± 6 and the group of cognitively normal seropositive individuals will have a mean percent M/Mφ activation of approximately 7 ± 2, a difference of 23 in mean percent M/Mφ activation (18). Based on these estimates, if we retain all 30 recruited individuals in these two groups, we will have a > 90% power to detect a significant difference in M/Mφ activation. Following the same assumptions, we would have a 90% power to detect a difference as small as 7.4 and an 80% power to detect a difference as small as 6.4. We do not anticipate a high attrition rate; however, if we lose 27% of the original 30 participants, we will still have a 90% power to detect a difference of 8.7 and an 80% power to detect a difference of 7.5 (table 3). Analyses will be completed comparing all enrolled participants (intent-to-treat analysis) as well as comparing groups with successful peripheral viral suppression at 6 and 12 months (viral load < 50 copies). We understand that the limited scope of this proposal may not allow power to fully compare macrophage activation and M/Mφ secretory products in individuals who succeed vs. fail therapy (not an aim of this proposal); however we hope to minimize failures through active interventions such as frequent contact by interim phone calls.

Power	MDD	Attrition Rate
80%	6.9	13%
80%	7.5	27%
80%	8.4	40%
90%	8.0	13%
90%	8.7	27%
90%	9.8	40%

Table 3: Anticipated power relative to attrition rate (rates reflect absolute numbers of patients loss to follow-up) MDD= Minimum Detectable Difference

The second endpoint for specific aim 1 is a composite neuropsychological score calculated as the mean of the norm adjusted NPZ scores. The association between M/Mφ activation and cognitive functioning is expected to be negative, i.e. a decrease in percent M/Mφ activation is expected to be associated with an increase in the composite neuropsychological test score. Assuming a sample size of 15 participants we will have an 80% power to detect a one-sided Pearson correlation of 0.62. It is also possible to include participants from our non-HAD group to compare change in M/Mφ activation with change in cognitive functioning. With a sample size of 30, we will have an 80% power to detect a one-side Pearson correlation as small as 0.16.

Proteomics The purpose of this analysis will be to identify candidates that may be of interest in future research. In this analysis, paired t-tests will be adjusted to control for the false discovery rate (FDR) rather than the family wise error rate (FWE) typically used in multiple comparison adjustment. While FWE controls for the probability of at least one rejection of a null hypothesis, the FDR is a measure of the expected proportion of falsely rejected null hypotheses among the rejected ones. A variety of procedures that make these adjustments have been developed recently to meet the specific statistical needs of genetic microarray data analyses (19, 20). The FDR-based methods are less

conservative and thus more powerful than controlling for FWE and are appropriate for this analysis. Analyses will be carried out using the *multtest* package of the suite of *bioconductor* packages from the statistical program R.

Limitations and contingencies: We anticipate no difficulty with the described assays, which have been performed by these investigators (including analyses completed on frozen and shipped specimens). Potential problems with acquisition of clinical data will be assessed monthly via VTC meetings. Our experience indicates that stated exclusion criteria should not be excessively burdensome. We anticipate 10 referrals to the Neurology clinic per month. Exclusion criteria will be re-examined to assess appropriateness; all screening data will be retained to facilitate this analysis. Feasibility data exists regarding utilization of our neuropsychological battery, however, we will monitor for complication and modify our approach if needed. With UH faculty on site in Thailand (Dr. Jerome Kim and Silvia Ratto-Kim), logistic issues regarding this study should be readily addressable.

A-2 – Hawaii AIDS Clinical Research Program

Hawaii AIDS Clinical Research Program,
University of Hawaii John A. Burns School of Medicine
Training and Research Infrastructure Development Activities in SE Asia

International HIV Training and Prevention Infrastructure Development Activities
In June of 2003, a Memorandum of Understanding (MOU) was signed between the Center of Excellence in Disaster Management and Humanitarian Assistance (Gerard Bradford III), the Department of Medicine, Tripler Army Medical Center (Col. Dale Vincent, Chief) and the University of Hawaii John A. Burns School of Medicine (Edwin Caman, Dean) to establish the collaborative working relationship between the COE and TAMC-DM/UH to develop and implement HIV/AIDS Prevention Education and Training activities in the U.S. Pacific Command's area of responsibility (USPACOM's AOR). Between 2003-2005, JABSOM faculty members (C. Shikuma, L. Kamemoto, L. Marten and C. Goshima) assisted as faculty in multiple COE sponsored SE Asia HIV workshops on various aspects of HIV/AIDS. The Workshops were held in Bangkok, Thailand, Hanoi, Vietnam and Pune, India.

JABSOM, together with AFRIMS, will now participate through the COE in the Vietnamese PEPFAR (President's Emergency Plan for AIDS Relief). JABSOM's specific role will be to train Vietnamese military physicians in HIV care and management including the appropriate use of HIV antiretroviral therapy. A UH PEPFAR faculty has been assembled, and a curriculum consisting of a series of 21 ppt presentations on various aspects of HIV care has been created and is being translated into Vietnamese. The training will be comprised of a 4 week course of intensive didactic teaching and clinic exposure – two weeks in Hawaii for didactic learning and to learn the fundamentals of antiretroviral care and management, and two weeks in Bangkok for intensive patient exposure and training in AIDS-defining opportunistic infection management. Two to three Vietnamese physicians will be trained each quarter. The first group of Vietnamese physicians is now scheduled to arrive in Honolulu in Jan 2006.

A small development grant from Gilead Pharmaceuticals has been received with the intent of training civilian physicians from various SE Asia countries in HIV care and management. To be headquartered in Bangkok, Thailand, it is anticipated that the training will occur in Bangkok as a central location within SE Asia for such training. The first trainees are anticipated in early 2006.

Research Infrastructure Development Activities
A cross-sectional NeuroAIDS protocol (UH-PMK NeuroAIDS Study 001: Predictors of Neuro-cognitive Decline and Survival in HIV-infected Subjects) was written and developed specifically to provide the mechanism to develop research infrastructure in Bangkok, Thailand. This pilot project was designed as a joint collaborative attempt between researchers at JABSOM, Phramongkutlao (PMK) Hospital and U.S.Armed Forces Research Institute of the Medical Sciences (AFRIMS). Consent forms were written, translated into Thai and certified independently to mirror the version written in

English. The protocol and informed consent documents were IRB approved by PMK as well as by UH. Administrative support and clinical research space were provided by PMK through the assistance of Dr. Suwicha (Tim) Chipatima, Director of International Affairs for PMK and laboratory support was provided by AFRIMS. A Thai research nurse was hired, and Dr. George Watt, who joined UH as a faculty member, provided the necessary oversight of the clinical and administrative operations. The study opened in August 2004, and in Dec 2005 completed its full initially determined target accrual of 45 subjects.

This cohort has been the basis of the following scientific abstracts either already presented or accepted for presentation:

> Valcour V, Nidhinandana S, Sithinamsuwan P, Thitivichianlert S, Apateerapong W, Ratto-Kim S, Kim J, Shiramizu B, Chitpatima S, Sukwit S, Chuenchitra T, Watt G; Robertson K; Paul R, Shikuma C. Neuropsychological Testing Abnormalities among HIV Patients in Bangkok, Thailand. Conference on HIV Infection and the Central Nervous System: Developed and Resource Limited Settings, Frascati, Italy June 2005
>
> Chuenchitra T, Sukwit S, Gonwong S, Shiramizu B, Ratto-Kim S, Sithinamsuwan P, Apateerapong W, Nitayaphan S, Kim J, Chitpatima S, Shikuma C, Valcour V, Nidhinandana S. The collaborative neuroAIDS research study in Thailand between the Armed forces Research Institute of the Medical Sciences, Royal Thai Army, Phramongkutkloa Medical Center, and the University of Hawaii: Laboratory research aspects. 15th annual Asia Pacific Military Medicine Conference (APMMC), Hanoi, Vietnam. May 2005
>
> Bruce Shiramizu, Samart Nidhinandana MD, Pasiri Sithinamsuwan MD, Thitivichianlert Sataporn MD, Wichitra Apateerapong RN, Silvia Ratto-Kim PhD, Suwicha Chitpatima PhD; Kevin Robertson PhD; Cecilia Shikuma MD, Victor Valcour MD, HIV DNA Correlates with HIV-1-Associated Dementia in Patients in Bangkok, Thailand, 13th Conference on Retroviruses & Opportunistic Infections, Denver CO, Feb 5-9, 2006.

Video-teleconferencing capabilities in place at Leahi Hospital, Honolulu, Hawaii and PMK, Bangkok, Thailand has been invaluable for the purposes of developing the international infrastructure in Bangkok. Teleconferences to discuss various aspects of the infrastructure and training/research activities occur between Honolulu and Bangkok faculty members and program staff on a weekly basis on Thursdays 2:30 pm Hawaii Time (Friday 7:30 am Bangkok time).

In 2005, an exciting new partnership with HIVNAT (HIV Netherlands Australia Thailand Research Collaboration) began. Our developing research infrastructure was given a name and will operate under the name SEARCH. A SEARCH website has been added under the Hawaii AIDS Clinical Research Program website: http://www.hawaii.edu/hacrp/search.htm. SEARCH partners include PMK, U.S.

AFRIMS, HIVNAT and UH. New SEARCH office space to house UH and AFRIMS personnel jointly will be opened on the grounds of HIVNAT/Thai Red Cross in April of 2006.

In addition to Drs. George Watt, Jerome Kim and Silvia Ratto-Kim (all of whom have faculty appointments with UH), two new faculty members will be joining the Bangkok UH faculty – Dr. Jintanat Anaworanich as Associate Professor of Medicine and Dr. Thira Woratanarat as Assistant Professor of Medicine. Dr. Jintanat will be directing the SEARCH clinical research operations and Dr. Thira will be directing the Gilead training project. Wichitra "Noi" Apateerapong RN, our original Thai RN in Thailand has re-located to Hawaii temporarily with the intent that she be trained in the conduct of ACTG clinical trials in preparation for opening of such trials in Bangkok. Other SEARCH personnel on site in Bangkok include a second RN, Benjawan Boonchkchai, hired to continue work on the NeuroAIDS project, Siriphan Gongwon (lab technician), Ninee Aranyanak (Program Coordinator for Gilead Project and Fon Varapon (Administrator/Fiscal Officer).

UH faculty (C. Shikuma M.D. and V. Valcour M.D.) have been invited to participate as a speaker and case discussion leaders for HIVNAT's highly regarded annual Bangkok Symposium on HIV Medicine to be held Jan 18-20, 2006. As this symposium is being viewed as the official announcement of the SEARCH collaboration, JABSOM Associate Dean Dr. Satoru Izutsu will be accompanying a group of 7 JABSOM faculty members to this symposium.

<u>SEARCH research/training international infrastructure has lead to the following grant proposals/projects:</u>

(Funded) **Macrophages, HAART, And HIV-1 dementia in Thailand**. (1 R21 MH072388-01) V. Valcour PI ***Funded, July 2004***
This awarded funding supports the longitudinal aspects of the original NeuroAIDS study; $300,000 total direct funding over 2 years.

(Pending) **Hawaii AIDS Clinical Trials Unit**, response to RFA-AI-05-002. C. Shikuma Proposed PI.
The research infrastructure developed in Bangkok was incorporated as part of this grant proposal for HIV vaccine and Optimization of Care clinical trials. If successful, total direct costs for UH is $2.3 million/year x 7 years. Review of grant is pending.

(Funded) **International HIV/AIDS Training Center** (Gilead Pharmaceutical)
This training center will be designed to train SE Asia civilian physicians in HIV/AIDS care and management. Initial group of trainees is scheduled for early 2006. Funded for total cost of $100,000.

(Funded) **President's Emergency Plan for AIDS Relief (PEPFAR)** (via Department of Defense CoE)

Funding will support training of 8-12 Vietnamese physicians in HIV care and management/year. Direct costs of approximately $210,000/ year x 5 years.

(Pending) **Safety, Tolerabilitiy and Immunogenicity of ACAM3000 Modified Vaccina Ankara (MVA) Small Pox Vaccine in HIV-Seropositive Subjects who are Vaccinia Naïve** (Acambis Pharmaceuticals) Review of proposal for SEARCH to open in Bangkok pending. Direct costs of approximately $200,000 total for study.

(Awarded) **HIV/AIDS Regional Training and Research Center in Asia** (Hui)
The funds support the University of Hawaii efforts to develop training and research infrastructure in HIV in Asia. Direct costs of approximately $300,000 x one year.

A-3 – Hawaii AIDS Clinical Trials Unit

Hawaii AIDS Clinical Trials Unit

The Hawaii AIDS Clinical Trials Unit (HACTU) is an integral part of the Hawaii AIDS Clinical Research Program (HACRP), a HIV clinical and translational research program of the John A. Burns School of Medicine (JABSOM), University of Hawaii – Manoa (UHM). Initially funded under a minority initiative in 1990, HACTU at Leahi Hospital in Honolulu Hawaii is now a fully established and experienced clinical trials unit of the Adult AIDS Clinical Trials Group (AACTG) that has consistently met the rigorous clinical trials standards of this organization. The site has community-wide support for its operations as the only clinical research program in Hawaii dedicated exclusively to HIV/AIDS and has a demonstrated ability to access Hawaii's ethnically diverse population, enrolling 34% of all nationally-enrolled subjects of Asian/Pacific Islander (API) descent since 1990 into AACTG studies. A research agenda for this Leahi site is now proposed that addresses not only the research agenda of the AIDS Clinical Trials Group (ACTG) network but the priority areas of preventive HIV vaccine and microbicides as well. A shared administrative and clinical trials infrastructure at this site will provide economy of scale. A clinical research site in Bangkok addressing HIV vaccines and optimization of care including co-morbidities is also proposed that builds on our program's newly established international therapeutic clinical research capability and the existing HIV vaccine expertise of the site.

(i). Overall Clinical Trials Unit and Administrative Structure

(i) A. Overview of Proposed Clinical Trials Unit (CTU) and Clinical Research Sites

This application is submitted by UHM to continue the Hawaii AIDS Clinical Trials Unit (HACTU) under the direction of Dr. Cecilia Shikuma as Unit Principal Investigator (PI). Two Clinical Research Sites are proposed for this Unit. The Sites, the Site Leader and the proposed Network/Priority Areas are described below:

Leahi Clinical Research Site Honolulu, Hawaii Site Leader: C. Shikuma Network/Priority Areas: • AIDS Clinical Trials Group (ACTG) Network • Vaccine Research and Development • Microbicides	**Bangkok Clinical Research Site** Bangkok, Thaila Site Leader: J. Ananworanich Network/Priority Areas: • Vaccine Research and Development • Optimization of Clinical Management, including Co-Morbidities

(i) B. Description of the Applicant Clinical Research Organization

University of Hawaii System, University of Hawaii – Manoa, and the John A. Burns School of Medicine

The University of Hawaii (UH) system is a 10 campus public system of higher education established and funded by the State of Hawaii. The various schools within this system are located throughout the six major islands that comprise the Hawaiian Islands. The University of Hawaii – Manoa (UHM) is the flagship of this UH system and is located in the Manoa valley of Honolulu. Currently, 20,4000 students are enrolled at

UHM in 87 bachelor's degree, 87 master's degree and 53 doctorate degree programs. Approximately 57% of its students are of Asian or Pacific Islander decent and 56% are women. According to the Chronicle of Higher Education, *UHM is the most diverse campus in the United States (US).*

The John A. Burns School of Medicine (JABSOM) is accredited by the Liaison Committee on Medical Education of the Association of American Medical Colleges and the Council on Medical Education of the American Medical Association, and annually accepts 62 students for entry into their MD program. Residency programs are offered in Internal Medicine, Pediatrics, Family Practice, Psychiatry, Ob/Gyn, and Surgery. In addition, JABSOM offers the MS and/or PhD degrees in biomedical sciences with concentrations in cell and molecular biology, clinical research, epidemiology, physiology, and tropical medicine.

Uniquely positioned by geography and cultural ties to Asia and the Pacific, the University of Hawaii seeks to serve as a bridge between the East and the West. International students from over 70 nations are represented on the UHM campus, which has conferred advanced degrees to internationally recognized leaders, such as Dr. Jong-Wook Lee, the current Director-General of the World Health Organization. In 1960 the US Congress established the East-West Center to strengthen relations between the US and the countries of the Asia Pacific region. This internationally recognized education and research organization is housed within the UHM campus. The UHM College of Business Administration offers a doctorate program in International Management, intended to develop high-level research and teaching skills in international management with a particular focus on Asia and the Pacific. UHM is a founding member of the Asia-Pacific Academic Consortium for Public Health, an independent non-profit corporation now with 44 member public health organizations in 18 Asia-Pacific nations established in 1984 to organize and support collaboration among academic public health institutions in Asia and the Pacific.

Overview of the Hawaii AIDS Clinical Trials Unit (HACTU) and the Leahi Clinical Research Site

The Hawaii AIDS Clinical Trials Unit (HACTU) is currently a main unit of the AACTG. Its primary site of operation is at Leahi Hospital. We now propose to continue the HACTU. Its current site of operation at Leahi Hospital will be proposed for HACTU as the Leahi Clinical Research Site. Dr. Shikuma will serve as Leahi Site Leader in addition to being PI of the HACTU. A second site is proposed in Bangkok.

HACTU shares clinical, basic science and translational resources with several other HIV-related research initiatives and programs under an umbrella program called the Hawaii AIDS Clinical Research Program (HACRP). This umbrella program currently combines the research expertise and funding of eleven researchers (C. Shikuma, V. Valcour, B. Shiramizu, M. Gerschenson, D. Chow, L. Kamemoto, L. Day, L. Marten, P. Kuo, Q. Yu and N. Hu) located at Leahi Hospital in Honolulu and five researchers (J. Kim, S. Ratto-Kim, G. Watt, J. Ananworanich, and T. Woratanarat) located in Bangkok, Thailand. HACRP's mission is: to bring trials of therapies for HIV and its complication to HIV-infected patients in Hawaii, 2) to participate in the HIV research mission of JABSOM, 3) to optimize HIV research, prevention and care efforts in Hawaii together with other University, State and Community groups, and 4) to participate, together with other international partners, in global efforts to promote HIV prevention, treatment and research.

The parent administrative and research headquarters of HACRP currently occupy 8,000 sq ft of space in 3 connected buildings (Young, Sinclair and Atherton buildings) of the Leahi Hospital complex. This space includes six examination rooms, a reception

room and the HACRP processing lab, all located on the ground floor of the Young Building in our Clint Spencer Clinic. With the exception of research pharmacy services, located approximately 5 miles away at Queen's Medical Center, all resources that enable a complete clinical trials operation are housed at Leahi. Six physician researchers (C. Shikuma, V. Valcour, B. Shiramizu, D. Chow, L. Kamemoto, and L. Day) participate in the assessment of patients enrolled in AACTG clinical trials within the Clint Spencer Clinic.

Four Research Laboratories are located adjacent to the Clint Spencer Clinic providing a translational research environment addressing HIV vaccine-related virologic and immunologic function (J. Kim and S. Ratto-Kim), macrophage function in response to HIV (B. Shiramizu) and HIV-associated mitochondrial dysfunction (M. Gerschenson). Drs. Kim and Ratto-Kim have temporarily relocated to Bangkok, Thailand to work for the US Armed Forces Research Institute of the Medical Sciences (AFRIMS), a major partner in our proposed Bangkok site. However, they retain their UH faculty appointment, and have fully functioning laboratories within Leahi Hospital. An Autonomic Laboratory (D. Chow), a room equipped for colposcopy/anoscopy procedures (L. Kamemoto) and a Metabolic Lab with a GE/Lunar Prodigy whole body dual energy absorptiometry (DEXA) machine complete the resources available within the Clint Spencer Clinic. Through contract services, the clinic also has an on-site neurologist (40% FTE) for complicated neurological studies and four trained HACRP research associates who can complete neuropsychological testing for HIV studies. HACRP operations at Leahi Hospital are supported by an active Community Advisory Board (CAB) as well as a community physician advisory board [Scientific Advisory Board (SAB)].

The Leahi site applies as a selected site of the ACTG network. In addition, our HACTU now proposes to address the HIV vaccines and microbicides priority areas as well. Substantial infrastructure in HIV immunology and vaccines was developed at UHM due to supplemental funding for an HIV Immunology and Vaccine Activity awarded by the National Center for Research Resources (NCRR) to JABSOM's Research Centers in Minority Institutions (RCMI) program. The goal of the UHM RCMI program is to develop research infrastructure at UHM; developing HIV vaccine infrastructure was a key specific aim of this supplement. HACRP already had some experience with HIV vaccine research as a site of the VaxGen trial. However, with this RCMI supplement, new capabilities in immune based assays were developed and a demographic survey was undertaken to determine the landscape in Hawaii for HIV vaccine clinical trials. Thus we are now well positioned to contribute both scientifically and as a clinical trials site to the field of HIV vaccines.

One of our physician-researchers at HACRP, Dr. L. Kamemoto, is a specialist in Obstetrics and Gynecology (Ob/Gyn) and a major contributor to this HIV Immunology and Vaccine Activity with specific emphasis on mucosal immunity. She provides colposcopy and anoscopy capabilities, as well as extensive contacts with Ob/Gyn and public health clinics. Thus our application to the microbicide field is based on our program's growing expertise in mucosal immunity, our on-site HIV Ob/GYN specialist and access to an appropriate patient base.

Bangkok Clinical Research Site

A Bangkok Clinical Research Site is proposed at the Royal Thai Army Clinical Research Center (RTACRC) of the Armed Forces Research Institute of the Medical Sciences (AFRIMS). As previously mentioned, two key UH faculty and HACRP researchers (Drs. Kim and Ratto-Kim) have temporarily relocated to AFRIMS while maintaining laboratories and faculty appointments at UH. This bridge provided an unmatched opportunity to pursue HIV research in Bangkok and several initiatives are

underway. The Bangkok Site will be administratively managed by HACTU but will draw on crucial support from 3 key consortium partners: AFRIMS, Phramongkutklao Medical Center (PMK) and the Thai Red Cross AIDS Research Centre (TRCARC)-affiliated HIV Netherlands-Australia-Thailand Research Collaboration (HIV-NAT). The Bangkok Site will be led by Dr. J. Ananworanich as Site Leader. She is an accomplished researcher from HIV-NAT with extensive background in HIV clinical trials management who has recently joined the UH faculty as Associate Professor of Medicine. Figure 1 describes the partners and their roles concerning the proposed Bangkok Site.

Briefly, the Bangkok Site will be operated administratively within HACTU as a UHM function. UHM will provide the Site Leader (Dr. J. Ananworanich) and the clinical staff for its operations (Thai nationals hired through UHM). AFRIMS provides an accomplished vaccine researcher, Dr. Sorachai Nitayaphan, to direct the vaccine effort and use of the RTACRC clinic facility for its operation and laboratory services (specimen processing/storage/shipment and HIV diagnostics). PMK provides a primary research patient base and key subspecialty researcher support continuing the collaborative relationship we have developed with Dr. Sataporn Thitivichianlert, Chief of Infectious Diseases and Dr. Samart Nidhinandana, Chief of Neurology. PMK will also provide administrative office space and access to their hospital lab for standard/safety labs. As PMK and AFRIMS are side-by-side, this will effectively be one site for all administrative and clinical needs. HIV-NAT will provide pharmacy and CAB support as well as technical and logistical assistance for the expansion of the clinical trials infrastructure at this site. *Commitment to the basic structure of this proposal and support for the success of this collaborative effort has been obtained from the highest levels and include Major General (Dr.) Suebpong Sangkharomya, Director General of AFRIMS; Col Carl Mason, Commander of US AFRIMS; Prof. Praphan Phanuphak MD PhD, Co-Director of HIV-NAT and Director of TRCARC; and COL Suwicha Chitpatima, Director, Office of Special Projects, Royal Thai Army, Phramongkutlao Medical Center.* Letters of support are included in the appendix.

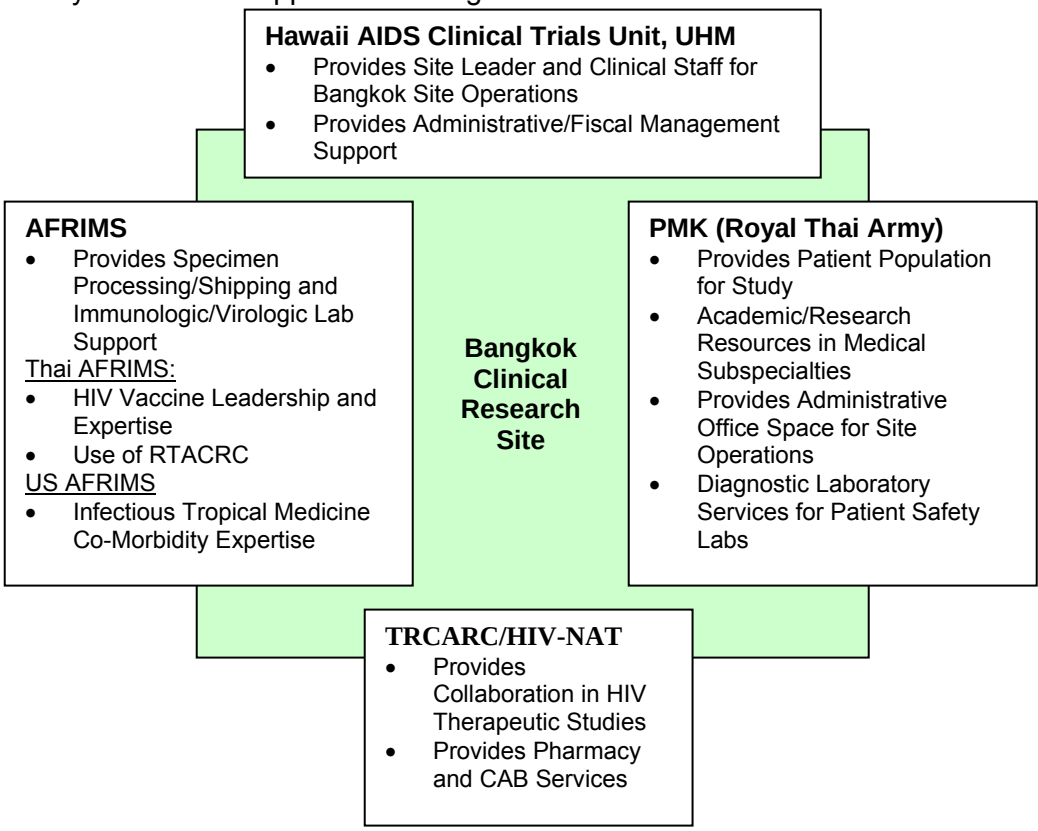


Figure 1: Contributions of each Consortium Member

This proposed Bangkok site is a natural extension of HACRP's existing HIV training and clinical research infrastructure, now 3 years in the making. The infrastructure grew from a collaborative relationship with a Memorandum of Understanding (MOU) between JABSOM, the Center of Excellence in Disaster Management and Humanitarian

Assistance (COE) of the US Department of Defense (DOD) and Tripler Army Medical Center in Honolulu to develop and implement "military to military" HIV/AIDS Prevention Education and Training activities in the US Pacific Command's area of responsibility. This MOU, which created the Joint Asia-Pacific HIV/AIDS Prevention Program, was co-signed by the then Dean of JABSOM, Edwin Cadman and is included in the Appendix. A series of HIV training workshops were held under this consortium utilizing PMK/AFRIMS as a central administrative and training hub in Southeast Asia. Researchers from HACRP provide most of the academic and HIV management training expertise for this consortium.

Our collaboration with the COE has now extended to include participation as a partner in Vietnam within the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). A training grant for Southeast Asian civilian physicians was secured by HACRP in 2005 from the Gilead Foundation. This further supports PMK/AFRIMS as a base of operations for HACRP. The temporary relocation of Drs. Kim and Ratto-Kim to AFRIMS in Bangkok to work in the DOD's HIV vaccine efforts resulted in further solidification of this effort. Such a presence of on-the-ground UH researchers have been instrumental in establishing our Bangkok infrastructure.

A clinical research component to the infrastructure was added with the opening of a NeuroAIDS clinical research protocol at this site in June of 2004. Developed and conducted in partnership with PMK's Neurology and ID faculty, the opening of this study provided an opportunity to work through all necessary regulatory, clinical, laboratory, and fiscal needs for a clinical protocol to be conducted in this international setting. The informed consent documents were translated into Thai (and verified independently to accurately reflect the English version) and the protocol and informed consent documents were submitted and approved by both the UH and the PMK Institutional Review Boards (IRBs). Administrative (PMK) and clinic space (AFRIMS) was secured and arrangements were made for laboratory processing (AFRIMS and PMK). A Thai Clinical Research Nurse (W. Apateerapong RN) and a supervisory physician-researcher (G. Watt MD) were hired. Thirty-six subjects have since been enrolled in this intensive longitudinal study. NIH-funding support has now been secured to continue this work [R21MH072388-01, PI V Valcour "Macrophages, HAART and HIV Dementia in Thailand]. Preliminary findings were presented at the HIV Infection and the Central Nervous System: Developed and Resource Limited Settings international meeting in Frascati, Italy in June 2005.

The proposed Bangkok site will now combine HACRP's newly developed clinical research infrastructure with the extensive HIV vaccine experience of this site. A joint facility of the U.S. Army and the Royal Thai Army, AFRIMS has conducted Phase I/II HIV vaccine trials and is a current site of the ambitious 16,000 n phase III prime boost ALVAC-HIV (vCP1521) and AIDSVAX B/E vaccine trial. AFRIMS's vaccine expertise is an integral aspect of this application with the basic scientific contribution from Dr. Kim, Chief of U.S. AFRIMS' Department of Retrovirology and HIV vaccine clinical trials expertise from COL Nitayaphan, Deputy Director General of Thai AFRIMS. Dr. Nitayaphan currently directs Thai AFRIMS' role in the joint US-Thai Army vaccine efforts. He will be HACTU's designated primary representative to the HIV vaccine research network. U.S. AFRIMS also provides specialized knowledge in various tropical infectious diseases likely to be significant co-morbidities in HIV-infected patients from Southeast Asia, including malaria, dengue, scrub typhus and hepatitis B, C and E.

Pharmacy and CAB support for this application will be provided by HIV-NAT in an exciting new collaborative partnership. HIV-NAT is a premier multi-centre research organization in Thailand with an extensive research network and expertise in HIV clinical

trials. Our new UH faculty member and proposed Site Leader for the Bangkok site, Dr. J. Ananworanich, comes from HIV-NAT, and HIV-NAT will also provide technical assistance for the efficient conduct of therapeutic clinical trials in Bangkok. Dr. Praphan Phanuphak, Director of the Thai Red Cross AIDS Research Centre and Co-Director of HIV-NAT, is a senior consultant on this application.

(i) C. Organization of the Hawaii Clinical Trials Unit (HACTU), University of Hawaii-Manoa (UHM)

Proposed External Administrative Structure for HACTU: Continuing its current structure, HACTU will remain administratively located directly under the Dean's office. This administrative location is reflective of the importance attributed to this program by the UH JABSOM administration. The Dean of JABSOM reports directly to the Chancellor of UHM, who in turn reports directly to the President of the UH System. The President is accountable for the affairs of the UH System to the UH Board of Regents.

Proposed Internal Administrative Structure of HACTU: The proposed internal administrative structure of HACTU is shown in Figure 2. Dr. Cecilia Shikuma, as PI, will provide global oversight for the activities of this Clinical Trials Unit. She will assume financial, administrative and regulatory responsibilities and overall accountability for the clinical trials operations. She will ensure adequate patient recruitment and retention, appropriate patient follow-up and toxicity management, good data management, accountability for study medications, and proper laboratory processing, storage and shipment at each of the 2 clinical research sites. Ms. Debra Ogata-Arakaki RN, our HACTU unit coordinator for 15 years, will provide unit coordination across the 2 sites and provide oversight of site compliance with network clinical trials management and DAIDS-mandated regulatory requirements. Mr. A. Lee, as the HACTU Administrator/Fiscal Officer, will ensure appropriate fiscal management and accountability of received funds at both sites.

Each site will have a Site Leader (SL), supported by an administrative staff, who will be responsible for the clinical trials operation of that site. At each site, a "Site Network Leader" (see Figure 3) will be appointed for each network represented at the site. This will usually be the researcher most interested in the research priority areas of that particular network. It will be his/her responsibility to ensure coordination of the network's scientific needs with that of the site. A coordinating committee will be formed at each site to advise the Site Leader. Membership will be comprised of the Site Leader, Site Network Leaders as well as other key personnel, such as the Site Coordinator, Pharmacist, Data Manager, QA/IRB Coordinator and Lab Supervisor, to ensure an integrated site response to the priorities of the various networks.

At the Leahi site, Dr. Shikuma will assume direct responsibilities as Site Leader and Ms. Debra Ogata-Arakaki will continue to provide specific oversight of the Leahi clinical trials site operations as Site Coordinator. Dr. J. Ananworanich will be the Site Leader at

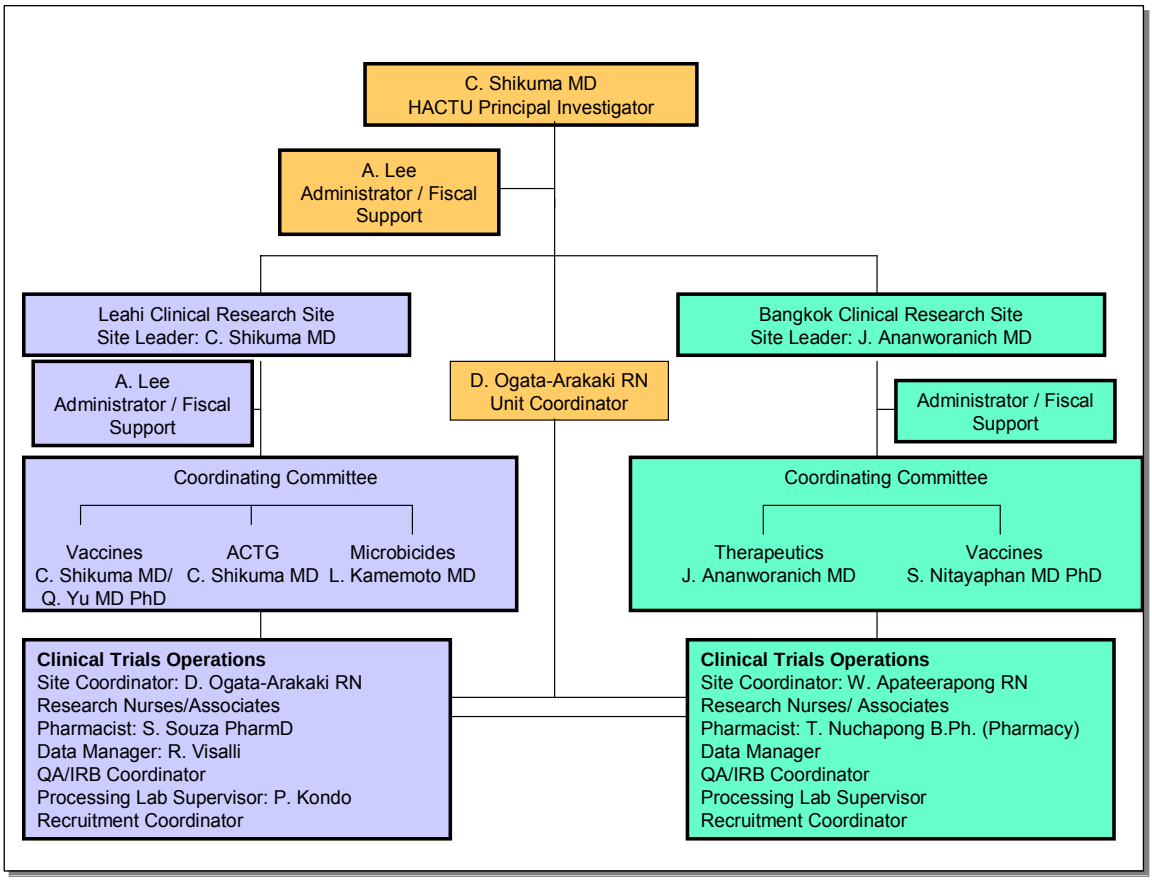


Figure 2: **Internal Administrative Structure of HACTU**

the Bangkok site. Ms. Wichitra Apateerapong, an experienced Clinical Research Nurse (CRN) originally from HIV-NAT and now the lead CRN for our Bangkok NeuroAIDS project, will be the Bangkok Site Coordinator. Ms. Apateerapong will transfer to our HACTU in Honolulu in July of 2005 for intensive exposure to ACTG-specific policies and requirements, operating as an ACTG CRN at this site. She will also be the chief study liaison between Honolulu and Bangkok. Thus, by the time of this grant's funding, she will have had an excellent background in Division of AIDS (DAIDS) and ACTG clinical trials operating procedures that will assist her in her new role as Bangkok Site Coordinator.

A very important aspect of clinical trials operations in resource limited settings is access to high quality support laboratories. The joint AFRIMS Department of Retrovirology HIV Clinical Research Laboratory is very closely integrated with the current effort through Dr. Kim, Chief of the Department of Retrovirology and UH faculty member. Importantly, this laboratory has an outstanding record in the processing, archiving, retrieval and shipping of specimens and is the only College of American Pathologists (CAP) certified laboratory in Southeast Asia. All assays (CD4, viral load, and hematology) are performed in this laboratory. Clinical chemistry and resistance testing will be added in October 2005. The laboratory has extensive experience in the use of advanced immunological assays for vaccine development. The experimental

expertise of this laboratory is now being used to develop laboratories in Tanzania, Kenya, Cameroon, Nigeria, and Uganda.

Relationship to Networks and Role of the Coordinating Committee: Dr. Shikuma and/or her designate will represent HACTU to each of the networks to which we are assigned. The responsibility of the HACTU Network Leader will be to represent the unit scientifically and to ensure that network priorities and needs are closely aligned with the activities and efforts at HACTU. Specifically, Dr. Shikuma will represent HACTU to the ACTG/ Optimization of Care Network, Dr. Nitayaphan will represent HACTU to the HIV Vaccine Network and Dr. L. Kamemoto will represent HACTU to the network responsible for Microbicides Research.

Both Leahi and Bangkok are proposed for Therapeutic (ACTG/Optimization of Care) and Vaccine Priority Areas. To provide maximum fluidity and success between the sites, we anticipate assignments for each site to coincide and specifically for the Bangkok site to receive ACTG assignment in accordance with HACTU's long-standing position as an AACTG site in Hawaii. Given the differing populations and research settings of our two sites, we will require the Network Leader representing each area to be familiar with and be able to represent site-specific needs. To facilitate this, frequent communications, both face-to-face and via video teleconferencing (VTC), are planned. VTC currently occurs on a weekly basis through a high-speed network connecting PMK to our conference room at Leahi Hospital. Each site will also have a specific individual assigned to each network's needs (Site Network Leader). This person will report to (or in some cases be) the HACTU Network Leader, further allowing full site-specific representation to the network and rapid implementation of the network scientific priorities at the site level. This proposed structure will thus allow timely bidirectional communications for optimal network-site integration as shown in the diagram.

Figure 3. Unit and Site Leaders for each Priority Area or Network

ACTG/ Optimization of Care

- HACTU Network Leader : C Shikuma MD (Leahi)
  - Leahi Site Network Leader: C. Shikuma MD
  - Bangkok Site Network Leader: J. Ananworanich MD

HIV Vaccines:

- HACTU Network Leader**:** S. Nitayaphan MD PhD
  - Leahi Site Network Leader: Q Yu MD Ph.D/ C. Shikuma MD
  - Bangkok Site Network Leader: S. Nitayaphan MD PhD

Microbicides:

- HACTU Network Leader: L Kamemoto MD MPH
  - Leahi Site Network Leader: L Kamemoto MD MPH

Each site's coordinating committee will match network priorities with site capabilities and function. It is envisioned that this committee will receive reports (via the Site Network Leader) on a regular basis from each network; discuss the desirability, feasibility and appropriateness of protocols proposed for opening at the site; monitor accrual, retention, manpower and logistical needs to advance the science of the Networks and take a leading role in establishing new links and resources needed to accomplish these goals. This may include the solicitation for involvement of other researchers with specific expertise needed for upcoming trials.

(i) D. Management and Communications Plan

Communication Plan

Communication between the HACTU Leadership/Leahi Site and the Bangkok site: The Bangkok site will be managed as a direct operation of UH/HACTU with important aspects secured in a consortium agreement. Close communications between Dr.

Shikuma and Dr. Ananworanich, between the HACTU Network Leader and the Site Network Leader at the other site, among investigators at both sites, between the site coordinators, and data management, laboratory and pharmacy teams will be integral to the efficient operations of this Clinical Trials Unit (CTU). It is estimated that investigator visits between the two sites are presently occurring at a minimum of every 2 months and we anticipate this will continue. Particularly in the early stages, frequent visits between Honolulu and Bangkok may be necessary not only for the site leaders but for pharmacy, administrative and laboratory personnel. As previously mentioned, VTC capability developed with the support of the U.S. DOD and the NCRR funded RCMI program at UH tie together HACRP's Fred Greenwood Conference Room at Leahi and the Conference Center at PMK. Currently PMK provides free technical support; there are also no costs associated with each connection. This allows this resource to be used frequently to maintain close communications between Honolulu and Bangkok with standing weekly conference calls held each Thursday at 2:30 pm Hawaii time (7:30 am Bangkok time on Friday). This weekly conference is attended by Investigators, clinical research nurses/associates (CRNs/CRAs), laboratory personnel and as needed by administrative staff on both sides. VTC has facilitated weekly updates on accrual in our NeuroAIDS project, timely discussion of protocol or patient management issues with our Thai research colleagues, trouble-shooting of laboratory issues brought up by our Thai laboratory coordinator Dr. Chuenchitra and prompt resolution of fiscal problems. It also enables Drs. Kim and Ratto-Kim in Bangkok to provide direct oversight over laboratory issues in their respective laboratories in Honolulu. Both Dr. Ananworanich and Ms. Apateerapong have demonstrated fluency in written and verbal English which assist in this communication process.

We intend to initiate a lecture series with Bangkok in coordination with standing HIV training lectures at Leahi using VTC. The existing lectures provide a broad spectrum of HIV care and management knowledge to the full HACTU staff in Hawaii. As the VTC provides a seamless means of simultaneously sharing PowerPoint slides between sites, adding an audience from Bangkok for these training conferences will be simple. Additional conferences, including our Wednesday afternoon journal club and visiting lecturers will be considered. Conferences from Bangkok that are in English can also be patched in to Hawaii to capitalize on cross-cultural training and maximize cross-site communication.

Leahi Within-Site Communications and Management: The Leahi site currently has an extremely effective communications and management SOP. As the incorporation of HIV vaccine and microbicide priority areas are an extension of work that already occur within the operational framework of HACRP and involves investigators already working together within the program, no problems that would require changes in the SOP are anticipated. Effective communication within the Leahi Research Site operations is facilitated by the centralized location of its operations with ready access to all parties involved. In particular, Dr. Shikuma's office is adjacent to that of Ms. Debbie Ogata-Arakaki, her unit/site coordinator, allowing immediate discussion of patient- or protocol-related issues on a day to day basis. Mr. Lee and the team of HACRP administrative assistants are immediately available in this same location and all investigators have their main research office on-site.

Bangkok Within-Site Communications and Management: Dr. Ananworanich will have overall responsibility for effective communications and management at the Bangkok site. Administrative staff, Ms. Apateerapong, Research Nurses, QA/IRB Coordinator and Data Manager will all be direct employees of UHM under her supervision in a centralized location in Bangkok. Since the planned within-site structure is consistent with HACRP's

existing structure at PMK/AFRIMS, a smooth transition is anticipated in adding the proposed structure on to the existing clinical research infrastructure. Ms. Apateerapong will provide direct day to day supervision of clinical personnel (clinical research nurses, QA/IRB coordinator and data manager) and coordinate pharmacy and laboratory services. Dr. Nitayaphan, who will be assuming a role as co-investigator and providing oversight for the HIV vaccine interests of the Bangkok site, works in the AFRIMS building and will be readily accessible for needed communications. Biweekly coordinating committee and weekly staff meetings will serve to formally bring all staff together on a regular basis to facilitate appropriate communication and management. A laboratory representative from AFRIMS Dept Retrovirology HIV Clinical Research Laboratory, and Ms. T Nuchapong, the pharmacist from HIV-NAT, will also regularly attend these meetings.

Decision-Making, Standard Operating Procedures, and Plans for Providing Effective Oversight

Decision Making Concerning Opening Protocols: At each site, the Site Network Leader will be responsible for submitting to the Coordinating Committee in advance of each committee meeting the protocol(s) that may warrant opening at that site. The protocol will be discussed in committee and the decision made based on scientific interest, feasibility, accrual potential, any real or potential conflicts with other open protocols and applicability to the site's population. As possible, HACTU expects to continue it's operating philosophy to participate as broadly as possible in the Networks' HIV scientific research agendas to maximize the research use of its sites' capabilities and to extend the research opportunities for the community population that it serves. The protocols will also be discussed with the CAB and their input factored into any decision made. The Site Leader will have the final decision on opening a particular protocol.

Implementation and Accrual of Protocols: Following the decision to open a protocol, the QA/IRB Coordinator will prepare the IRB documents. In Bangkok, this will require protocol and informed consent translation to Thai. Certification of the translation accuracy is currently accomplished by the AFRIMS QA-QC department. They (AFRIMS) will continue to provide this service to the Bangkok site as a consortium partner in this endeavor A recruitment plan will be constructed by the Recruitment Coordinator. The Site Coordinator will assign the protocol to a clinical research nurse who will be responsible for the implementation and coordination of all protocol mandated visits and procedures, and for the creation of protocol specific tools. All needed Case Report Forms (CRFs) will be ordered by the data manager. A local "start up" meeting will be held for each protocol prior to implementation involving all physician-researchers, research nurses, pharmacist, data manager and laboratory personnel. As the Bangkok site includes UH faculty, all protocols will need to be reviewed both by the Thai IRB and UH IRB. This has been very straight forward with our existing protocol and can easily be coordinated through VTC and email.

A monthly accrual report with research subjects enrolled into each open protocol will be generated, reviewed and monitored by the Coordinating Committee. Difficulties with accrual and/or feasibility aspects of each protocol will be discussed and plans constructed for improvements. Decisions to terminate a specific protocol will be made by the Site Leader in consultation with the Coordinating Committee.

Decision Making Concerning Oversight of Clinical Trials Operations: The Site Leader is responsible for the clinical trials operation at the site level and will be responsible for the hiring, on-going training, and monitoring of personnel to insure the smooth operations of the clinical trials infrastructure. It is anticipated that sites will be evaluated by the Networks on various aspects of clinical trials management (i.e. timeliness of IRB

submission, reporting of SAEs, accrual of subjects, data management, laboratory processing, shipment and storage, pharmacy storage and accountability for study meds). Site evaluation of performance will be discussed at the Coordinating Committee and plans for correction of deficiencies constructed. The Site Leader will be responsible for the implementation of these corrections. All Network site evaluations will be monitored by Dr. Shikuma as PI of this Unit. She will insure that appropriate and timely assistance is available to correct any deficiencies associated with the clinical trials infrastructure at either sites.

Effective Oversight of Clinical, Laboratory, Pharmacy and Data Management Aspects of the Clinical Trials Infrastructure in Bangkok: Especially in the beginning the unit coordinator and experienced members of the pharmacy, data management and laboratory personnel of the Leahi site will assist in assuring compliance with DAIDS regulations involving IRB approval and consent documents, appropriate management of patient visits and CRFs, laboratory processing, laboratory shipment and storage, and pharmacy regulations. Both Dr. Ananworanich and Ms. Apateerapong are experienced in clinical trials work; the HIV-NAT Pharmacy and AFRIMS Retrovirology Lab have an impressive tract record of excellence; therefore it is anticipated that the only assistance that may be required may be integrating the site operations with specific Standard Operation Procedures (SOPs) as mandated by DAIDS or the Networks.

Bangkok-Specific Procedures to ensure Timely Regulatory Approvals by Local and National Authorities for Drug Importation, Specimen Shipping and Clinical Study Implementation

Drug Importation: Importation of both investigational/non-investigational drugs and vaccines is the responsibility of the site pharmacist. HIV-NAT is familiar with the procedure and the authorities involved and can ensure a timely procurement of drugs. When an order is placed, HIV-NAT contacts and obtains product shipment information from the manufacturer for submission to the Thai Food and Drug Administration for an import permit. Once an import permit is issued, it is submitted to the Thai Customs office for permission to import with tax exemption. A courier service is then contacted by HIV-NAT to handle transporting of the shipment from the airport cargo to HIV-NAT.

Specimen shipping: Specimen shipment in this application will be handled by the Retrovirology Lab at AFRIMS. Specimens processed and archived at AFRIMS for natural history and vaccine studies number in the hundreds of thousands. These specimens have been shipped to the United States (including Hawaii) in liquid nitrogen "dry shippers." Processing times are typically under 3 hours; viability on frozen samples is usually greater than 90%, even when shipped to the United States. Frozen samples from these studies have been analyzed successfully in the U.S. and used to support an End-of Phase II package for the vaccine candidates currently in Phase III testing. The Specimen Processing laboratory and standard operating procedures at AFRIMS have been reviewed by DAIDS prior to initiation of the DAIDS funded Phase III trial. SOPs for Specimen Processing are maintained in Infotrove by the QA section of the Department of Retrovirology, AFRIMS, under Dr. Robert Paris. Modifications and Version Control are by SOP and are consistent with College of American Pathologists (CAP) requirements. Specimens are archived using the Specimen Processing System (SPS) system used in the Phase III trial that creates barcoded samples and permits real-time monitoring of current specimen archives. The SPS system was reviewed for 21CFR11 compliance by the U.S. Army Medical Research and Materiel Command. All personnel involved are properly trained and certified in Shipping Infectious and Biological Substances by IATA/DOT with required recertification documented every other year.

Clinical Study Implementation: As previously mentioned, protocol and informed consent translation to Thai will be necessary prior to IRB submission and accomplished by on-site English to Thai translation capability, with verification of translation accuracy by the QA-QC office in AFRIMS. IRB approval of protocols which do not involve the use of investigational drugs or vaccines will be accomplished by the Royal Thai Army IRB which holds a Federal Wide Assurance from the Office of Human Research Protection (OHRP; FWA #00001813). The IRB meets 1-2 times per month and approval can be expected to take 1-2 months. Protocols involving investigational drugs or vaccines are, in addition, submitted to a 2nd IRB (usually the Thai Ministry of Public Health IRB) which may then take 2-3 months for approval. UH IRB approval will be submitted concurrently.

(i) E. Principal Investigator and Other Key Staff

The experience and scientific contributions of the PI, Unit Coordinator, Bangkok Site Leader, and Network Leaders are described in this section. Other key researchers who bring key expertise to HACTU are described in the respective (iv) A "Leahi Clinical Research Site" or (iv) B "Bangkok Clinical Research Site" section of this proposal.

Cecilia M. Shikuma MD, HACTU PI and Leahi Site Leader, is Professor of Medicine at JABSOM and is a boarded Infectious Diseases specialist who has focused her efforts on HIV clinical research since joining HACTU in 1992. Under Dr. Shikuma's leadership, the HIV program which now operates as HACRP has grown from a program with 2 full-time physician researchers to that involving 7 full-time physician researchers and 4 basic science researchers on site at Leahi and an additional 4 physician-researchers and one Ph.D. researcher in Bangkok. Originally funded as a minority institution site by the National Institute of Health (NIH) with set-aside funding, she has successfully recompeted the HACTU twice as an AACTG site without minority institution protection. She currently assumes an additional leadership role as Program Director of the NeuroAIDS Specialized Neuroscience Research Program (SNRP), a program grant funded by the National Institute of Neurologic Diseases and Stroke (NINDS) to develop NeuroAIDS research infrastructure for UHM. She is also currently Activity Leader for the HIV Immunology and Vaccine Core Activity within the NCRR-funded RCMI program, a position she assumed following the relocation of Dr. Kim to Bangkok. She has contributed scientifically both outside and within the AACTG system particularly in the metabolic/mitochondrial field. She has been a member of the AACTG Executive Committee, chair or co-chair of 4 AACTG protocols, chair of the Metabolic Subcommittee and co-chair of the Mitochondrial Focus Group. She has published on the role of mitochondrial toxicity in HIV-associated lipodystrophy and currently has NIH-funding to explore potential therapies for this syndrome and the role of ATP depletion in its pathogenesis.

Debra Ogata-Arakaki RN ACRN, HACTU Unit Coordinator, is an accomplished coordinator who has been with HACTU since its inception. Under her guidance, the HACTU-Leahi site has matured into an experienced clinical trials unit. She was instrumental in helping to establish the HACTU in 1990 following 4 years as an HIV clinical specialist/research study coordinator working with Dr. Henry Masur at the NIH. She participated as a reviewer in the NIH Study Section for the Pediatric AIDS Clinical Trials Unit recompetition in 1996 and is a past member of the AACTG Site Operations Working Group as well as the Site and Data Management Committee. She was elected as the first Study Coordinator representative to the AACTG Immunology Research Agenda Committee (RAC). She has been a field representative for numerous past ACTG studies, and is currently still active as a field representative on A5051 and A5024. Locally, she has been responsible for all regulatory affairs for HACTU, and has utilized

her knowledge of regulatory guidelines as a member of the UHM IRB for the past 8 years.

Jintanat Ananworanich MD, Bangkok Clinical Research Site Leader, is Associate Professor of Medicine at JABSOM. She has extensive expertise in HIV clinical trials in adults and in children. For the past 5 years, she has worked as project leader for 12 studies in adults and children at HIV-NAT and the TRCARC overseeing a total patient population of almost 1000 and a total budget of 7 million USD. The adult studies under her leadership include a large structured treatment interruption (STI) study, Staccato, which has enrolled 436 Thai patients, and studies on resistance to protease inhibitors and pharmacokinetic (PK) studies. She was successful in obtaining a large NIH U19 CIPRA grant and is now leading this study of when to start antiretroviral (ARV) therapy in 300 children in Thailand and in Cambodia. She is American Board Certified in Pediatrics, Allergy and Immunology, and Clinical and Laboratory Immunology. She has published extensively with 8 peer-reviewed publications this year. She serves as a lecturer for the Immunology Section, Department of Medicine at Chulalongkorn University. She also is a regular speaker for UNICEF, WHO, UNAIDS, the Thai Infectious Diseases Society and the Thai AIDS Society. She was a member of the expert panel to develop the 2004 Thai national guidelines for HIV treatment and of the Track B International Committee for the XV (2004) International AIDS Conference, and she is currently a member of the HIV subcommittee for the American Academy of Allergy and Immunology.

Dr. Ananworanich is currently a clinical trials physician at HIV-NAT and has now accepted a position with UHM as Associate Professor of Medicine working with HACRP. In the mutual interests of both HIV-NAT and HACRP, both parties signed a Memorandum of Understanding (MOU) [enclosed in Appendix] regarding a transition plan for Dr. Ananworanich's time. From December 2005, she will coordinate HIV trials in Bangkok on behalf of UHM at 75% FTE and specifically, will assume the position as Site Leader of the HACTU Bangkok Clinical Research Site at 30% FTE if the UHM's grant proposal is successful. She will continue to spend 25% of her time on project management for IMPAACT network studies for HIV-NAT until appropriate coverage for her position is found and a smooth transition of her current responsibilities can been accomplished. It is anticipated that this can be accomplished within one year's time.

Sorachai Nitayaphan MD, PhD, HACTU HIV Vaccine Network Leader and Co-Investigator at the Bangkok Site, is one of the leading HIV vaccine researchers in Thailand and is the Deputy Commander of AFRIMS. COL Nitayaphan is a founding member of the Thai AIDS Vaccine Evaluation Group (TAVEG); both he and Dr. Kim are current members of the Executive committee of that organization. Dr. Nitayaphan has been an investigator or principal investigator in 5 HIV vaccine trials in Thailand – gp120 SF2 (RV99); bivalent gp120 SF2/CM235 (RV114); ALVAC-HIV (vCP1521) subtype E prime with AIDSVAX B/E boost (R135); the Phase III trial of vCP1521 + AIDSVAX B/E (RV144); and the Merck Adenovirus trial. He was also a part of the TAVEG Executive Committee for RV132 (vCP1521 prime + Chiron gp120 SF2/CM235 bivalent boost). COL Nitayaphan has published extensively on the epidemiology and pathogenesis of HIV in Thailand in addition to publications related to HIV vaccines. He is Laboratory Senior Investigator on the DAIDS sponsored trial of vCP1521 + AIDSVAX B/E. He is also Director of the RTACRC, the proposed clinic to be utilized for this submission.

Lori E. Kamemoto MD, MPH, HACTU Microbicides Network Leader and Co-investigator at the Leahi Site, is an Assistant Professor of Obstetrics & Gynecology (Ob/Gyn), Medicine and Public Health at JABSOM, and is a board certified Obstetrician/Gynecologist. She has clinical expertise in human papillomavirus (HPV)

and lower female genital tract and anal disease, leads the Cervical and Vulvovaginal Disease Clinic at Kapiolani Hospital's Women's Cancer Center, as well as the Cervical, Vulvovaginal and Anal Disease Clinic for HIV infected men and women at our Leahi site. In addition to her expertise in the evaluation of female genital tract mucosa, she is currently one of less than 20 providers in the U.S. who have received training in the evaluation of anal HPV disease with the use of high resolution anoscopy. She has contributed to the national HIV infected women's health research agenda by serving on the AACTG Women's Health Committee, AACTG's Gender and Antiretrovirals Working Group, NIH sponsored Fertility Regulation and Hormones in HIV infected Women Conference Planning Committee, and as protocol Chair of two AACTG women's studies, the most recent an innovative study on the contraceptive patch system in HIV infected women. She serves on the American Society for Colposcopy and Cervical Pathology education committee, has been an abstract reviewer and presenter at HIV conferences and NIH meetings, and is PI of several pharmaceutical sponsored HPV vaccine studies. In her capacity as Associate Clinical Director of the RCMI HIV Immunology and Vaccine Core Activity, she is currently working on the mucosal immunology of HPV disease in HIV infected men and women.

LTC Jerome Kim MD, Senior Consultant to HACTU at both the Leahi and Bangkok Sites for the HIV Vaccine Priority Area, is Chief of the Department of Retrovirology, AFRIMS and concurrently Associate Professor of Medicine at JABSOM. He has experience in the writing and execution of Phase I – III HIV vaccine trials and is currently the U.S. Army Sponsor representative in Thailand, supervising the execution of the DAIDS sponsored Phase III trial [1-6]. He has been chief of both the CD4 T helper cell laboratory and the neutralizing antibody laboratories in the Division of Retrovirology, Walter Reed Army Institute of Research. Dr. Kim has been an investigator on 3 Phase I/II therapeutic HIV vaccine trials and 7 HIV vaccine trials. He has written 3 prime boost HIV vaccine trials: 1) RV124 (vCP205 + oligomeric gp160/MN-LAI-2); 2) RV132 (vCP1521 + gp120 SF2/CM235 or gp160 TH023); and 3) RV135 (vCP1521 + gp120 MN/A244). He was on the Protocol Committee for RV144 and RV148, the DAIDS sponsored Phase III trial, and was sent to Thailand in 2002 to ensure that the trial started in a timely fashion. Then coming to JABSOM, he wrote and successfully received funding for the RCMI Hawaii HIV Immunology and Vaccine Core Activity. In late 2004, Dr. Kim was asked back to Thailand to manage the Thai Phase III trial and assumed his current position. He plans to return to Hawaii when his obligations in regards to this Phase III trial are over. He currently serves as the Chairperson of the Executive Committee of TAVEG. Dr. Kim continues to run his Neutralizing Antibody laboratory at JABSOM and has permission from the military to be a basic science/laboratory consultant to HACTU for this application. Thus, his scientific/laboratory expertise is offered in this application through his position as Associate Professor of Medicine in JABSOM. Through frequent trips to Hawaii, conference calls, and VTC, the strong historical link between AFRIMS and the HACRP will serve as the coordinating nexus of the planned collaboration. Dr. Kim will bridge the two efforts and is expected to play a major role at both vaccine sites.

Praphan Phanuphak MD PhD, Senior Consultant to HACTU is Professor of Medicine and Microbiology, Faculty of Medicine, Chulalongkorn University in Bangkok. He is Director, TRCARC, and Co-Director of HIV-NAT. His impressive credentials include Membership in the Steering Committee on Clinical Research and Drug Development, Global Program on AIDS, WHO, and current President of the Thai AIDS Society. Especially in respect to the Bangkok Site operations for the Optimization of Care priority

area, Dr. Phanuphak will lend expert advice on important technical aspects of this clinical trials endeavor.

(i) F. Rationale for the Selection and Expected Contribution of Site

Leahi, the site of our HACTU operations for the past 15 years, applies as a site selected by the ACTG Network. We propose this site based on its long tract record of excellence in therapeutic clinical trials management and strength of our scientific contributions within the Adult ACTG system. This site represents our state's interest in contributing as an equal partner to the national/international efforts against HIV/AIDS. This site will provide HIV trial access to its ethnically diverse population including individuals of Asian Pacific Islander and specifically of Native Hawaiian descent. The site will broadly implement a diverse range of protocols within the ACTG's research agenda. Furthermore it proposes to contribute its unique scientific expertise in the long term complications of HIV (including metabolic/mitochondrial, NeuroAIDS and aging issues), women's issues, and novel immune strategies to further the research aims of this Network. In addition, the site proposes to now utilize its existing clinical trials capabilities and its extensive community contacts to participate in the HIV vaccine and microbicides research fields, in so doing providing an economy of scale in clinical trials infrastructure. The newly developed basic science infrastructure in HIV vaccine research and the existing on site expertise in gynecology and anoscopy add to the ability of the Leahi site to successfully conduct the necessary research in these fields.

In keeping with our cultural and geographic ties to Asia, our program already has substantial research and training interests at the proposed Bangkok site. This site is proposed on the basis of HACRP's strong commitment to develop this research site and the successfully developed new clinical research infrastructure on site as evidenced by the successful launching of its first clinical protocol. We further build on the extensive HIV vaccine clinical trials tract record of Dr. Nitayaphan's group at Thai AFRIMS, access to a CAP-certified laboratory and to the tropical infectious disease strengths at AFRIMS, and the strength of our collaborators (AFRIMS, HIV-NAT, PMK)'s. The success of this site is assured by the superb credentials in HIV clinical trials management of the proposed Site Leader, J. Ananworanich and our Site Coordinator, W. Apateerapong.

(ii) Contribution to Network Clinical Research Plans.

Site-specific protocol participation capabilities are described under the respective Site sections - (iv) A.4 Leahi "Site Contribution to Network and Priority Areas" and (iv) B.4 Bangkok "Site Contribution to Priority Areas". The sites' unique ability to contribute to these Priority Research Areas/Network and future scientific contribution capabilities of the sites are described below by Network/Priority Area.

(ii) A. Vaccine Research and Development (Leahi and Bangkok)

The Leahi site: The Leahi site anticipates that its major contribution to the HIV Vaccine field will be in the area of smaller, earlier phase I/II clinical trials testing new and innovative approaches that show high promise in preclinical development. Within the AACTG therapeutic arena, the *Leahi site has excelled in the conduct of small intensive Phase I and II studies* often requiring intensive monitoring, complex toxicity management, novel procedures or advanced immunologic assays. This capability can easily be adapted to the conduct of Phase I and II trials in HIV vaccines, allowing efficient and cost-effective use of Leahi's established clinical trials infrastructure. Host factors including HLA type may influence outcome, and access to various representative populations at a domestic level (such as that available in Hawaii) may be desirable.

While it is likely that the overwhelming majority of participants in phase III HIV vaccine trials will be from international areas severely impacted by HIV/AIDS and not

from domestic sites*, it is important that the full spectrum of individuals in the US population at risk for HIV/AIDS be represented in such research.* Epidemiologic assessment done by our program in Hawaii suggests that [MSM] and [females of Asian Pacific Islander descent who have other risk factors] represent our current "at-risk" populations. These "at-risk" categories include the population of particular relevance for Hawaii – the Asian Pacific Islander ethnic community. While still small, the number of Asian Pacific Islanders living with AIDS in the US increased from 1,253 to 3,826 individuals (a 305% increase) between 1993 to 2003. As voiced by Dr. Fauci, Director of NIAID, during the 2005 National Asian and Pacific Islander HIV/AIDS Awareness Day, "It is essential that Asians and Pacific Islanders be involved in HIV/AIDS clinical trials so that we can learn if drug regimens or vaccine candidates work in these populations."

In 2003, supplemental funding from NCRR (2 G12RR03061-19, S Shomaker [PI]) successfully applied for by Dr. Kim to develop a HIV Immunology and Vaccine Core Activity within the RCMI program made possible the development of HIV vaccine research infrastructure within JABSOM. Funds were used to establish the capability to perform a wide array of immunologic assays including, but not limited to, neutralizing antibodies (Nabs), HIV-specific CD4+ T cell proliferation, and CD8+ cytotoxic T cell (CTL) activity. Dr. Kim's laboratory previously provided support for Nab evaluations of several products in HIV vaccine prime-boost studies [4-6], and his lab at Leahi has continued this practice, providing support for Nab analysis for an AACTG study on STI (A5170), and for a collaboration with Dr. M. Schnell at Thomas Jefferson University investigating a rhabdovirus prime/boost strategy designed to induce both cellular and humoral immune responses to HIV-1 envelope antigens [7]. Dr. S. Ratto-Kim has published extensively on T helper cell induction in HIV vaccines (therapeutic and prophylactic) [2, 8-20] and is an international leader in the analysis of epitope specific T helper cell responses to vaccination [12]. Drs. J Kim and S. Ratto-Kim were involved in the discussions of the use of CD3/CD28 expanded, non-specific T helper cells as a way to reconstitute CD4 helper cell activity [3]. Dr. Ratto-Kim assisted in the characterization of a novel dendritic cell based HIV vaccine [11]. The initial suggestions of the potential utility of IL-7 in HIV infection were posited in studies from this group [18]. Dr. Q. Yu who will be joining the HACRP program in Honolulu in Sept 2005 has studied the role of CD40 ligand (CD40L) and Ox40-ligation to activate and mature dendritic cells and enhance CD8+ T cell cytotoxic (CTL) response [21-24]. These scientific strengths can be offered to the Network responsive to the HIV vaccine priority area.

It can be argued that a successful HIV vaccine would have to confer protection against the virus not only against intravenous viral transmission but transmission that occurs at the major mucosal sites of entry as well, such as the vaginal and rectal mucosa. In a combined effort involving Drs. L Kamemoto (Ob/Gyn physician), and Dr. A. Imrie's (Cytotoxic T Cell Lab) and Dr. J. Kim's (NAb Lab) laboratories, the HIV Immunology and Vaccine Core Activity is currently involved in efforts to reproducibly conduct immune assays on cervical/vaginal and rectal lavage samples and to correlate these findings with those from the patient's blood specimens. In our hands, we have been able to measure CD4 and CD8 cells by flow cytometry and to detect neutralizing antibodies in these specimens.

Finally, tremendous synergy is possible both at the level of the investigator and at the protocol implementation level in linking HIV vaccine and therapeutics research infrastructures together. A natural synergy and opportunity exists for the testing of candidate vaccines as immunomodulator therapy in HIV infected individuals. A center that is experienced in the evaluation and management of HIV and its complications is

ideal to monitor and follow potential modifications of the natural host response that can occur as a result of vaccine administration.

Finally, the dynamics that result from tying the Leahi and Bangkok sites together has tremendous value in enhancing the scientific expertise on both sites and in establishing collaborative research partnerships as well as in promoting the development of researchers in training. Drs Kim and Ratto-Kim's involvement which spans across the Leahi and Bangkok sites will serve as an important bridge in tying together the expertise at both sites.

Bangkok Site: The Bangkok site has tremendous experience in HIV vaccine trial execution. Through Dr. J. Kim and Dr. S. Nitayaphan , the HACTU-Bangkok site brings substantial HIV vaccine clinical expertise through all phases (Phase I-III) of studies.

AFRIMS (US and Thai) has contributed substantially to the characterization of the Thai HIV epidemic. These contributions range from epidemiology, definition of risk factors, characterization of the serologic and genotypic characteristics of the virus, definition of the natural killer and ADCC activities, neutralizing antibody, and cellular immune responses. Three of the 4 subtype CRF01_AE vaccines are derived from strains isolated by Thai and US AFRIMS scientists. These scientists have also been involved in the initial description of the raging heterosexual epidemic in young Thai men, the first description of a recombinant virus (CRF01_AE), and the first documentation of dual HIV infection. The Thai and US components have figured prominently in the planning and implementation of the current phase III HIV vaccine trial, which began in September, 2002 in Rayong and Chonburi Provinces east of Bangkok (Dr. Kim is Sponsor Liaison and Dr. Sorachai is the Laboratory Senior Investigator). Four phase I/II vaccine protocols (with a total of 580 enrollees) involving AFRIMS have been conducted. The joint AFRIMS Retrovirology Laboratory will provide access to the only CAP-certified laboratory in HIV diagnostics in Thailand. The US and Thai components of AFRIMS will soon be participating in 2 new HIV vaccine protocols through the US Military HIV Research Program - a new subtype CRF01_AE MVA vaccine (RV158) and an in-depth immunologic analysis of vaccine induced immune responses using the same vaccine combination (prime-boost) as is used in the Phase III trial.

Evaluation of the on-going epidemic in Thailand, as will be described in section (iv) B.1 "Description of the Site Environment and Patient Catchment Area" suggests that 3 "high risk" groups warrant specific attention –intravenous drug users, MSM and discordant couples. Though categorized in other areas, the utility of discordant couples studies in HIV vaccine testing should not be under emphasized. The availability of antiretroviral testing and CAP certified laboratories removes much of the ethical quandary facing studies of discordant couples. All three groups are cohorts that are unlikely to be the focus of the U.S. military's HIV vaccine efforts in Thailand. Should studies be undertaken in these high risk categories, our proposal will link the important HIV vaccine trials expertise of Thai AFRIMS and the sophisticated virologic and immunologic capabilities of the joint AFRIMS Retrovirology Lab with the HIV Vaccine Network's efforts in these subpopulations. The Leahi site may be able to contribute its growing expertise in mucosal immunity in studies of HIV transmission in MSM.

The tremendous HIV vaccine expertise of this site will allow intellectual cross-fertilization in efforts to identify potential candidate vaccines appropriate not only for preventive vaccine work but as immunomodulators for HIV infected individuals as well. Linking HIV vaccine and therapeutic efforts will provide the opportunity to enhance enrollment or follow-up in studies of discordant couples or longitudinal studies of HIV seronegative individual who seroconvert.

(ii) B. AIDS Clinical Trials Group (Leahi)

The ACTG Network's proposed therapeutic research agenda span 5 of the 6 priority areas listed in the Network Leadership RFA (Translational Research, Optimization of Care, HIV Vaccines, Maternal-Child Transmission and HIV Prevention*).* The Leahi section of this application [(iv) A.2] details our planned protocol participation by these priority areas. As the research needs mandated by the HIV epidemic have evolved, our protocol participation has also evolved to accommodate the increasingly complex nature of AACTG clinical trials. We have developed, for example, the capability to conduct dual energy absorptiometry (DEXA) scanning, peripheral nerve/subcutaneous fat biopsies and endothelial dysfunction assessment. We view our "adaptability" as an asset that we offer to the ACTG Network in this grant application.

Specific scientific expertise is also offered to the ACTG Network in the following high priority research areas:

- Long Term Complications of HIV and its Therapies: The long-term consequences of HIV and its therapies are likely to be of increasing importance in developed countries. While potent antiretroviral therapy has extended the life-expectancy of HIV-infected patients and substantially decreased the occurrence of AIDS-defining illnesses, the rate of death in HIV-infected patients in the U.S. is still higher than that of the general population. While many factors may account for this phenomenon, studies done to ascertain the reasons for death in the era of HAART reveal a substantial increase (now accounting for >50% of deaths) in non-AIDS related deaths, particularly those related to cardiovascular and liver related complications [25-27]. The ACTG Network proposes a bold therapeutic research agenda to optimize the clinical management of HIV disease. To "evaluate the long-term toxicities" in the optimization of clinical management and "to study the pathogenesis of …complications related to ART…and other co-morbidities of HIV" is part of the ACTG Network's high priority areas.

The Leahi site proposes to play a critical role in this high priority area by contributing our scientific expertise in the areas of dyslipidemia, insulin resistance/diabetes, mitochondrial toxicity, non-alcoholic steatohepatitis, neurocognitive dysfunction and aging. Research will be needed not only to find effective therapeutic and preventive management for these long term complications but to evaluate antiretroviral regimens for such toxicity risk. Toxicity risk in respect to special populations (i.e. non-white ethnicity, female gender, and those co-infected with hepatitis C or B) will also need to be considered. There are few data on the safety of ARV drugs during pregnancy despite the increasing use of combination therapy during pregnancy.

Finally, the CDC estimates that by the year 2015, 50% of the population in the U.S. living with HIV/AIDS will be >50 years of age. It is likely that our aging HIV population will be particularly impacted by these long-term toxicities. As an example, our site recently published information that suggests that neurocognitive dysfunction may be present in nearly 2/3 of our older HIV population [> 50 yrs of age, includes patients with HIV-associated dementia (HAD, 25%) and Minor Cognitive Motor Disorder (MCMD, 45%)] [28, 29]. Thus, research on the differential impact of such toxicities in our aging population and how such toxicities may be identified, prevented and treated will be important research issues for the future.

Our site is well positioned to assist in these toxicity areas. Our researchers have published extensively in the area of wasting and lipodystrophy [30-32], metabolic/mitochondrial dysfunction [32-40], insulin resistance and diabetes [33, 36, 41], hypertension [42], and neurocognitive and peripheral nerve dysfunction [29, 33, 43-45]. Dr. Shikuma has chaired the AACTG Metabolic Subcommittee as well as Mitochondrial Dysfunction Focus Group. She is currently taking the lead in analyzing the metabolic impact of various antiretroviral regimens initiated in 1100 antiretroviral naïve subjects in

A5095. Dr. Gerschenson conducted the landmark NRTI-toxicity studies in the animal model [37-40], has been chair of the ACTG Genomics Focus Group, is a current member of the Cardiovascular Subcommittee, and directs the official mitochondrial laboratory for the AACTG. This laboratory has extensive capabilities for morphological, biochemical, and genetic mitochondrial and nuclear studies as well as a capacity to assay oxidative stress markers. Additionally, the laboratory has access to resources for genomics (SNP analysis), microarray, and proteomics, and we anticipate proposing studies to clarify the role of mitochondrial polymorphism in NRTI-induced toxicities such as lipodystrophy and peripheral neuropathy. Dr. Chow has published on the effect of HAART on blood pressure [42], and is chair of A5209 which will determine the efficacy of ezetimibe on LDL cholesterol elevations in HIV infected patients. Dr. Valcour is a member of the Neurology AIDS Research Consortium (NARC) and the AACTG Neurology Subcommittee and is PI of the largest HIV cohort study in the US focused on age and neurocognitive function. (Neurocognitive Function: HIV Seropositivity and Aging - funded by NINDS/NIH U54 NS4 3049). He chairs AACTG 5157, a study to evaluate Acetyl-L-Carnitine as a novel therapy for dideoxynucleoside reverse transcriptase inhibitor-associated peripheral neuropathy. Newer research on potential long term complications have focused on sleep disturbances (Hawaii Community Foundation, PI K Fast/ V Valcour) and the effect of HIV and ARV on exercise tolerance (RCMI Clinical Research Center grant, PI: L Day).

■ Women's Issues: Women constitute 22% of people living with AIDS in the US and more than 50% in many parts of the world. Despite such statistics, too little is known about female physiology and the differential influences of HIV, anti-HIV drugs and anti-HIV-related side-effects on this system. Hormonal changes during the menstrual cycle, pregnancy and menopause may influence drug absorption, and anti-HIV drugs may interact with contraceptive and other hormonal therapies. Women may be more likely to experience certain ARV-related toxicities including fat accumulation, breast enlargement, hepatic steatosis and osteoporosis. HIV infected women have high rates of infection with HPV infection, with an associated increase in condyloma, precancer and cancer of the lower female genital tract.

Dr. Kamemoto is currently Chair of an Adult ACTG protocol A5188, a pharmacokinetic study of the effect of LPV/r on transdermal and oral contraceptive hormones. Our site also has specific expertise in HPV, and lower female genital tract and anal diseases as Dr. Kamemoto runs a cervical and vulvovaginal disease referral clinic and has had additional training in the evaluation of anal HPV disease with Dr. J. Palefsky (UCSF). In addition, Dr. Shikuma, as Chair of the Metabolic Subcommittee has advised the A5084 team on study design aspect of metabolic toxicities associated with pregnancies. Our site hopes to continue to offer such expertise to the ACTG Network's scientific agenda.

■ Immunologic Studies: Immunology expertise developed within our recent vaccine initiative will have applicability to the ACTG agenda, and our site proposes to participate scientifically in these areas. As previously explained, Drs Kim and Ratto-Kim have been involved in novel concepts in immunomodulatory therapy, including the use of CD3/CD28 expanded, non-specific T helper cells [3], a novel dendritic cell based HIV vaccine [11], and use of IL-7 [18] and rhabdovirus prime/boost strategy [7]. Dr. Q Yu has been involved in the role of CD40 ligand (CD40L) and Ox40-ligation to enhance CD8+ T cell cytotoxic responses [21-24].

Dr. Kamemoto together with the laboratories of Dr. Kim and Imrie have detected cytotoxic T cell and neutralizing antibody responses within vaginal and anal lavage fluid of HIV+ subjects. Such assays may have utility in assessing the effect of systemic

antiretrovirals (ARV), immune-based therapy, or co-morbid STDs on local mucosal HIV immune function. Dr. Kuo is funded to study CD4 T cell responses against HIV in the setting of drug treatment and drug resistance to identify mechanisms and correlates of protection against HIV. Dr. Shiramizu has research expertise in the role of HIV infected monocytes and macrophages in HIV associated dementia. Pilot studies of certain compounds (such CCR-5 inhibitors or compounds that prevent activation of monocytes/ macrophages) for the treatment of HIV dementia are planned, and if successful may be proposed to the ACTG for larger scale trials.

(ii) C. Optimization of Clinical Management, including Co-Morbidities (Bangkok)

The Bangkok Clinical Research site is an ideal site for studies on the optimization of clinical management. While situated in a developing country with many clinical and co-morbidity issues common to these regions, this site has researcher expertise and laboratory sophistication that matches or exceeds those of domestic HIV clinical trials sites. This site will offer Dr. Ananworanich's extensive expertise in scientific ARV strategy research. She has most recently been involved in studies designed to understand the role of STI and the impact of PK parameters in optimizing ARV clinical care. This site's link with the AFRIMS research laboratories will allow a dynamic interaction with basic science laboratories to translate pathogenesis findings into clinical studies. Participation by Thai patients with predominately CRF01_AE recombinant virus can add information about the differential role of HIV-1 subtypes on host immune responses and ARV resistance patterns. Concerns regarding the low resistance threshold, reproductive toxicity and ethnic variation in pharmacokinetics of NNRTIs have recently led to interests in studying quadruple NRTI therapy as an alternative to NNRTI-based initial therapy in resource poor settings. Considering the mitochondrial toxicity potential of NRTI medications, studies of such heavily weighted NRTI therapies may lend themselves to linking the mitochondrial expertise at the Leahi site with optimization of therapy expertise at the Bangkok site.

The high rates of certain opportunistic infections found in Bangkok will allow studies of cost effective therapy for cryptococcal meningitis and MAC disease. The high rate of co-infection with hepatitis B (HBV), hepatitis C (HCV) or both (8.7%, 7.2% and 0.4% respectively [46] in Bangkok) will allow co-infection studies addressing the tolerability and PK of new ARV regimens in this population, the role of host cellular immune responses and host genetics on long-term outcome and treatment success, the significance of different HBV and HCV viral variants, and optimization of HCV and HBV prevention and therapy.

AFRIMS provides specific capabilities that offer unique opportunities for studying HIV co-morbidities. An improved understanding of the interactions between malaria and HIV/AIDS is recognized as a crucial area of focus for several major international programs such as the Global Fund. Malaria is the major disease studied by the Department of Immunology at AFRIMS with investigations that range from the examination of the basic molecular biology and immunology of the plasmodium parasite to the understanding of malaria drug and vaccine development. The Department of Enteric Diseases is a world leader in developing rapid and accurate diagnostic techniques for the etiologic agents of diarrheal disease. Work done in Nepal by AFRIMS first identified cryptosporidium as an important cause of traveler's diarrhea. This organism, as well as others being investigated by the Department of Enteric Diseases, has been identified as a major cause of persistent diarrhea in adults with HIV-1 infection.

(ii) D. Microbicides Priority Area (Leahi)

In the absence of a completely efficacious HIV vaccine, topical microbicides represent an important strategy in the prevention of HIV transmission through sexual

intercourse, the most common means of HIV transmission. The Leahi site proposes to contribute to the microbicides priority area in the conduct of Phase I/II safety and early efficacy studies of microbicides in both HIV uninfected and HIV infected individuals. HACTU will contribute to the scientific agenda not only in cervicovaginal microbicide safety evaluations but also in anorectal safety evaluations. HACTU's cervicovaginal disease expert (L. Kamemoto) has obtained additional training in high resolution anoscopy and biopsies for the evaluation of anal HPV disease in men and women. With our site's juxtaposition of investigators with female genital tract and anorectal clinical expertise, immunology and virologic laboratory expertise (including CD4, CD8 and neutralizing antibody laboratories), infectious disease/HIV specialist physicians, as well as a physician with specific STD expertise (A Katz), HACTU is in a strong position to contribute scientifically to the Microbicide Network. Dr. Kamemoto is currently leading a study, in collaboration with Drs. Imrie, Kim, and Goodman (Cancer Research Center of Hawaii) on the mucosal correlates associated with HPV infection in HIV-infected men and women. A MSM partner study of HPV infection is planned. In addition, we have been able to measure HIV neutralizing antibodies and quantitate CD4/CD8 cell numbers in cervicovaginal and anal lavage specimens. We are in the process of standardize the assays. This ability may eventually contribute to microbicide and vaccine objectives. Drs. Yu and Hu will contribute their knowledge of dendritic cell – CD4/CD8 cell interactions. These investigations may play a role in developing a model of natural cervicovaginal and anorectal mucosal defenses and the evaluation of local immune responses in those who become HIV infected.

(iii). Community Interactions

HACTU strongly believes in community partnership in its research endeavors. Due to the physical distance and differing needs of the two populations served by HACTU's two sites, 2 separate Community Advisory Boards (CABs) are planned. Each is described in their respective site sections. Each will directly advise the Site Leader and Clinical Team for that particular site. Administrative support for their function will be integrated within the administrative budget at each site. The guiding principles for CAB membership and function include: 1) CAB membership should reflect the local community population that the site serves; 2) the CAB should function to review protocols, provide community input on research functions, assist with outreach and recruitment, and provide community representation at the Network Level; 3) the site's operation needs to operate as part of the local community; with this in mind, the site leadership needs to communicate regularly with the CAB and other community representatives regarding the community's perspective on protocols offered for enrollment and regarding its global role in the community

(iv) Clinical Research Sites

(iv) A. LEAHI Clinical Research Site (Honolulu, HI)

(iv) A.1 Description of the Clinical Research Site

Description of Site Environment and Patient Catchment Area

The Islands of Hawaii: Hawaii, constituting the 50th state of the U.S., consists of a chain of 8 main islands located 2,397 miles west of San Francisco. There are roughly 6,420 sq miles of land encompassing the islands with a total population of 1,257,600 individuals, 80% of which reside on the island of Oahu with the remainder of the rest of the population mostly on three other islands - the Big Island of

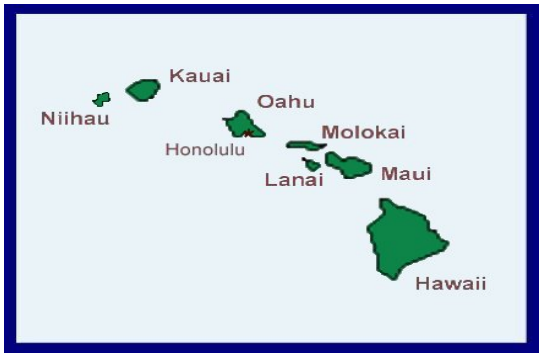


Figure 4: The Islands of Hawaii

Hawaii, Maui and Kauai. The general ethnic composition of the state, according to the 2000 U.S. Census Bureau (redistributed using 1990 data acquisition methodology by the Department of Health for reporting consistency) was 65.9% APIs (with 8.6% Hawaiian), 31.4% white, 0.4% Am Indian/Alaska Native, and 7.2% Hispanic Origin [47].

The HIV Population in Hawaii: The patient catchment area for the Leahi site is the entire State of Hawaii. According to the Hawaii Department of Health HIV/AIDS Surveillance Semi-Annual Report, 2,779 cumulative cases of AIDS have been reported as of December 31, 2004. Reflecting population densities, the majority of AIDS cases were reported from Oahu (73%) with the remainder divided among the three outer island counties. Based on CDC guidelines for calculations using newly diagnosed AIDS cases, *it is estimated that between 2,600 to 2,900 HIV-infected people live in Hawaii.* Hawaii now collects HIV infection data (as opposed to AIDS data) by unique identifiers. However because of concerns regarding completeness of data collection, HIV data has not been released.

The demographics of HIV in Hawaii reflect similar but slower trends to those reported nationally. The majority of cases are still seen Caucasian men, and MSM; however, there are steady increases in the proportion represented by women, heterosexual exposure, and minority ethnic groups, in particular the Native Hawaiian/part Hawaiian population. These changes are evident in the differences between total cumulative (1983-2003) AIDS cases diagnosed and those in the most recent five-year period for which data are available (1999 to 2003). Women made up 7.5% of cumulative cases and 12.1% of cases in the last five year period. Heterosexual transmission accounted for 5.4% of cumulative cases and 8.4% of cases in the last five years. APIs made up 27.6% of cumulative cases and 33% of cases in the last five year period.

These state data can reliably be used to obtain an overall picture of the general demographics of the HIV participants that can be recruited into HIV therapeutic trials. By gender, 90.9% were male and 9.1% female. By ethnicity 63.6% were Caucasians; however there is significant representation of minority populations including APIs (23.6%), Hispanics (5.4%), African American (6.6%), and others (0.9%) [47]. Representative recruitment is exemplified by our Aging with HIV Cohort Study, where the demographic profile of the 250+ cohort members matches that of the state statistics by age, gender, ethnicity and island representation.

In assessing HIV risk in seronegatives, *2* populations may warrant special attention as being particularly “high-risk” for HIV infection.

- Men who have Sex with Men (MSM): MSM behavior is the most frequently reported AIDS risk factor accounting for 73.6% of all cases diagnosed from 1983 to 2003 in Hawaii [47]. The overall numbers of AIDS cases related to MSM has decreased over time for all race/ethnic groups except for the Hawaiian population. The majority of cases (74%) were reported from Oahu. STD surveillance data may provide information about trends in high-risk sexual behavior. Syphilis, like AIDS, has disproportionately affected the MSM population in Hawaii. The incidence of syphilis among MSM declined sharply in the 1980’s and remained at low levels through the late 1990’s. From 2001 to 2003 there was a resurgence of syphilis among MSM, with 33 cases in this period compared to 6 cases in the previous three year period. Among cases from 2001 to 2003 with known syphilis status, 52% were co-infected with HIV, raising concerns that this may represent an increase in high-risk sexual behavior among the MSM population in Hawaii.
- Women of Asian-Pacific Islander descent with other risk factors: In Hawaii, from 1983-Dec 2003, 214 AIDS cases in females were diagnosed. By risk factor 47.7% reported heterosexual contact and 31.2% IDU. Women were diagnosed with AIDS

at younger ages than men, with 42.5% of women diagnosed under the age of 35 compared to 32.2% of men. Almost half (45.8%) are Asian Pacific Islanders [with 18% Hawaiians]. Contracting other STDs indicates risk behavior that may expose people to HIV and it is pertinent that rates of Chlamydia infection in Hawaii is the third highest in the nation (663/100,000 in 2003 compared to national average of 467/100,000). Like HIV, Chlamydia has particularly affected women of younger ages (65% of cases under 25 years) and Asian Pacific Islanders (75% of cases).

While APIs remain underrepresented in Hawaii's HIV/AIDS epidemic, this is *not* true for the Native Hawaiian/part Hawaiian population. *Native Hawaiians/part Hawaiians accounted for 13.2% of AIDS cases diagnosed from 1999 to 2003, exceeding their 8.6%* reported in the general population for APIs *[48].* In 2000-2001, the rate of AIDS cases reported for Hawaiians was 34.7/100,000 population while Native Hawaiian/ part Hawaiians represent only half that rate of the total population (18.2 per 100,000). *This is of particular concern as a Health Disparity issue* since Native Hawaiians also have one of the highest rates in Hawaii for hypertension, stroke and cerebrovascular conditions, diabetes and cancer [49-52]. Moreover, they are less likely to receive proper prenatal care and account for over half of all teens giving births (mothers age <19 yrs) [51, 53]. HACTU is the only site nationally or internationally that can reliably assure representation of this important population into HIV clinical trials.

HACTU Leahi Clinical Research Site: The HACTU site operates within the Hawaii AIDS Clinical Research Program (HACRP), an HIV clinical and translational research program of the School of Medicine. HACRP is located within 3 buildings (Young, Atherton and Sinclair) at Leahi Hospital in Honolulu on the southeastern coastline of the island of Oahu. Leahi hospital is 5 miles from the administrative offices of JABSOM at Kakaako and 3 miles from the main UHM campus.

Dr. Shikuma's office and all clinical staff (Site Coordinator, 3 additional RNS, 2 RAs, one Data Manager (DM) and one Data Assistant) are located on the 5th and 6th floors of the Young Building. Patients are seen in the Clint Spencer Clinic, located on the ground floor. This clinic provides a reception room and 6 fully equipped exam rooms. Study-mandated minor procedures (lumbar punctures, genital secretion collection) and minor surgery (subcutaneous fat biopsies) are performed in this clinic.. The clinic houses a GE Prodigy Lunar whole-body DEXA scanner. One exam room is equipped with a comfortable phlebotomy/lounge chair and TV for extended PK studies. The processing laboratory is conveniently located within the Clinic premises. The research pharmacy is 5 miles away at Queen's Medical Center (QMC), the main tertiary medical care hospital in Honolulu. This arrangement has worked well for our program as it provides appropriate drug storage and back-up pharmacy support. QMC facilities are also utilized for the majority of our other imaging and procedure needs (Ultrasound, MRI, Liver Biopsy, Carotid Duplex Studies). Drs. Shikuma, Day and Chow maintain hospital privileges at the Queen's Medical Center and this hospital is utilized for all our inpatient needs.

Figure 5: Location of Leahi Hospital in respect to UHM campus, Kakaako JABSOM campus and Queen's Med Cntr

Other Clinical and Research Efforts within HACRP: Other research initiatives currently

active within HACRP help to support the translational research interests of HACRP and provide expertise to the national AACTG research agenda. This includes the NIND-funded longitudinal cohort study of 250 HIV patients with 250 matched controls. This *Hawaii Aging with HIV Cohort Study* is designed to study the impact of aging on HIV neurocognitive function (V Valcour), to determine the role of HIV integration and macrophage activation on HIV neurocognitive disorders (B Shiramizu), and to support various studies relating to the role of mitochondrial dysfunction in lipoatrophy (C Shikuma and M Gerschenson). Other active research projects include the development of brain cell models to evaluate the effect of HIV and ARV toxicity (M Gerschenson), the investigation of autonomic dysfunction in lipodystrophy (D Chow), the evaluation of HIV specific T cell responses and activation/dysregulation of monocytes/macrophages (S Ratto-Kim), the determination of humoral immune responses to HIV envelope antigens following rhabdovirus prime/boost vaccine and after STI (J. Kim). More recent initiatives have further investigated HPV and mucosal immunity (L Kamemoto), exercise dysfunction and CPK Elevations in HIV (L Day), and sleep dysregulation in HIV (K Fast).

Currently, 4 basic science research laboratories operate within HACRP - the Hawaii HIV and Immunobiology Lab (B. Shiramizu M.D.) Molecular Medicine and Infectious Disease Laboratory (M. Gerschenson Ph.D.), and both the Neutralization Laboratory (J. Kim M.D.) and CD4 Laboratory (S. Ratto-Kim M.D.) of the Hawaii HIV Immunology and Vaccine Activity. New predominantly wet lab space (5,500 sq ft) on the 2nd floor of the Atherton building will add further needed space to the program this fall, through an arrangement negotiated by the Dean of JABSOM. It is anticipated that the area will be occupied, before this funding begins, by the relocated laboratories of Drs. J Kim and S. Ratto-Kim (from the Young building basement) and by the new laboratories of Drs. Q. Yu, N. Hu and P Kuo. The vacated spaces in the Young building basement will be utilized to accommodate the growing space needs of the patient care and research clinics as well as the expanding HACRP/HACTU processing lab.

Weekly operational and clinical research staff meetings, teaching conferences, research/journal club, special seminars/guest lectures as well as monthly meetings of the CAB and SAB are held in the Fred Greenwood Conference Room in the Atherton Building. This room is equipped with VTC capabilities allowing remote viewing of the weekly JABSOM Medicine grand rounds and weekly VTC with the Bangkok site. The VTC has also been used to directly interface with NIH when needed, avoiding costly travel.

In Jan 2004, an HIV specialty clinic was launched within the Clint Spencer Clinic with the full support of the SAB HIV community physicians. This clinic fills the need for HIV specialty care in the Oahu community and also serves as an HIV teaching forum for JABSOM medical students/residents. Patients are referred from community physician's offices, AIDS service organization (ASOs) and STD clinics. Drs. Shikuma, Chow, Kamemoto and Day currently staff this clinic , providing a composite full-time clinic with 24-hour access to physicians. In a little over one year since its opening, the clinic has grown to encompass approximately 150 active patients. A ½ day clinic/month is held by Dr. Shikuma in Hilo, on the island of Hawaii, adding an additional 50 patients to the patient census. An additional ½ day Kona clinic is planned.

(iv) A.2. Overall Site Leader and other Key Personnel

Cecilia M. Shikuma MD, Site Leader. Dr. Shikuma will function as both the Site Leader for the Leahi Site and Principal Investigator for this grant (see section (i) E for full description)

Debra Ogata-Arakaki RN, Site Coordinator. Ms. Ogata-Arakaki will continue to manage the Leahi Site (in a role now renamed "Site Coordinator") in addition to her new role as Unit Coordinator providing oversight over both the Bangkok and Leahi sites (see section (iv) E for full description)

Scott Souza PharmD, Site Pharmacist. Dr. Souza has 15 yrs of experience as the HACTU/Leahi Site Pharmacist. Under his direction, the HACTU research pharmacy services have consistently met and excelled in the high standards of research pharmacy operations mandated by DAIDS.

Jerome Kim MD, Senior Consultant, See section (i) E for description.

Lori Kamemoto MD, MPH, Co-Investigator and HACTU Microbicides Network Leader. See description in Section (i) E.

Qigui Yu, MD/PhD, Co-Investigator and Leahi Site HIV Vaccine Network Co-Leader, is Assistant Professor of Medicine. He has been involved in research on the use of human CD154 (CD40L)-expressing ALVAC virus as molecular adjuvants to enhance HIV-1 specific memory CTL responses by dendritic cells. He is also interested in understanding the role of Neisseria gonorrhea and HPV to impair dendritic cell maturation and subsequent HIV specific T cell immunity. He will provide oversight over the Leahi Site Processing Laboratory and participate scientifically as the Leahi Site HIV Vaccine Network Co-Leader.

Mariana Gerschenson PhD, Co-Investigator, is Associate Professor of Medicine, and Cell and Molecular Biology. At HACRP she is the Director of the Laboratory of Molecular Medicine and Infectious Diseases. Her laboratory has been selected by the Complications of HIV RAC as the AACTG recommended laboratory for mitochondrial assays since 2002. Dr. Gerschenson is an accomplished investigator who has extensively assisted the AACTG in research surrounding complications potentially secondary to NRTI-induced mitochondrial toxicity. She will participate scientifically to research at HACTU.

Victor Valcour MD, Co-Investigator, is Associate Professor of Geriatric Medicine and Neuroscience focusing on HIV-related neurological and neurocognitive disorders as well as the impact of age on HIV complications. He is a member of the AACTG's Neurological subcommittee of the Complications RAC and Chair for the only currently open HIV neuropathy trial within the AACTG (ACTG 5157). His *Hawaii Aging with HIV Cohort* is currently the largest longitudinal HIV aging cohort in the US that is focused on age and cognition [29, 33, 45]. He also conducts an international dementia trial to evaluate novel markers of dementia using proteomics and 4-color flow cytometry in Bangkok, Thailand (NIMH funded) [33], has provided neurological expertise to the U.S. Pacific Command's Joint Asia Pacific HIV/AIDS Prevention Program, and has trained neurologists in Bangkok concerning HIV dementia assessment. He will assist in the clinical care of research patients.

Dominic Chow MD MPH, Co-Investigator, is Associate Professor of Medicine and Pediatrics. He is Deputy Director for the University of Hawaii Combined Internal Medicine and Pediatrics Residency Program. He is an accomplished researcher who has been a member of AACTG's Outcomes Committee and later the Resource Use & Cost Effectiveness Subcommittee. He has focused his research interests on the metabolic, cardiovascular and autonomic dysfunctions associated with HIV and its complications. He is the Co-Chair of A5209 studying the role of Ezetimibe in HIV dyslipidemia. He has published on blood pressure elevations that has occurred in the era of HAART [42]. He is Director of the Autonomic Laboratory at HACRP and is funded for a RCMI project studying autonomic dysfunction associated with HIV infection and its

therapies and the role it may play in cardiovascular dysfunction. He will assist in the clinical care of research patients.

Bruce Shiramizu M.D., Co-Investigator is Professor of Pediatrics and Medicine. Within the AACTG, Dr. Shiramizu was Chair of ACTG 5096 assessing the use of SPECT as a Non-Invasive Alternative to Liver Biopsies in HCV/HIV infected patients [54]. He was PI of the UH subsite for the University of California, San Francisco (L Kaplan, PI) AIDS Malignancy Consortium. He has published on the role of macrophages in neurocognitive dysfunction and aging [43, 55] and aids in our community relations through work with numerous AIDS service organizations. He will assist in the clinical care of research patients.

Silvia Ratto-Kim PhD, Co-Investigator, See section (iv) B.2.

Larry Day MD, Co-Investigator, is board certified in Internal Medicine and Infectious Diseases and is Assistant Professor of Medicine. He assists in the evaluation and monitoring of research patients on study and participates in providing specialty care for HIV infected patients in the Clint Spencer Clinic. He will assist in the clinical care of research patients.

Lisa Marten PhD, Co-Investigator, is Assistant Professor of Medicine. She has a Doctorate in Public Health from Columbia University and a Masters in Public Policy from Harvard John F. Kennedy School of Government, and will serves as our program's epidemiologist to facilitate the Leahi site's studies.

Al Katz MD, Co-Investigator, is Associate Professor of Public Health Sciences and Epidemiology and Medical Director of the Diamond Head STD Clinic, State of Hawaii Department of Health. He has published on sexual behaviors and gonococcal and chlamydial infections in Hawaii [56-58]. He is past Chair of the UH IRB. He will assist in the targeting of HIV high risk populations through his knowledge of the epidemiology of HIV and STDs in Hawaii, and in his role as Director of the Diamond Head STD Clinic.

Philip Kuo MD PhD, Co-Investigator, is Instructor in Medicine at JABSOM. He is currently on sabbatical for an Allergy/Immunology fellowship at the National Jewish Medical Center/University of Colorado program returning to Hawaii in July 2006, and is working in the laboratory of Dr. Cara Wilson of the University of Colorado. His current research focus relates to CD4 T cell responses against HIV in the setting of drug treatment and drug resistance. He will assist in the clinical care of research patients.

Other Significant Contributors who have agreed to provide scientific and logistical support for this effort

Allison Imrie PhD, Co-Investigator, is Assistant Professor of Public Health Sciences and Epidemiology. She has specific expertise in cytotoxic T cell mediated assays and the role of compartment specific immune function particularly within cerebrospinal fluid.

Ningjie Hu PhD, Co-Investigator, is Instructor in Medicine. She brings further immunologic capability to the site including flow cytometry, ELISA and lymphocyte proliferation assay expertise.

Lynette E. Kagihara DDS, MSED, Co-Investigator, is Associate Professor, and Director of the Oral Health Research and Education for JABSOM. She was Director of Advanced Education in General Dentistry for the University of Southern California School of Dentistry prior to her relocation to JABSOM. She is interested in HIV-related oral disease and will be a collaborator in oral health research.

Michael Watters MD, Co-Investigator, is Professor of Medicine who brings neurologic expertise to this effort.

Mark Goodman PhD, Co-Investigator, is Researcher with the Hawaii Cancer Center. He will provide his expertise on HPV and dysplasia to this effort.

(iv) A.3. Clinical Trials Infrastructure

Leahi's site operations and management have evolved and adapted to meet the AACTG's increasingly more complex and diverse research protocols. This adaptability speaks well for the site's ability to now effectively expand trials capabilities to the areas of vaccine and microbicide research. The strength of the unit lies in its dedicated and experienced staff. The low turn over of key staff [Site Coordinator D. Ogata-Arakaki RN (15 yrs), CRNs N. Hanks RN and C. Milne RN (12 yrs), DM R. Visalli (7 yrs), Site Pharmacist S. Souza (15 yrs), and Processing Laboratory Supervisor P. Kondo (15 yrs)] has provided program stability and continuity of care for our patients.

Clinical Infrastructure: Leahi operations will continue under the administrative direction of Dr. Cecilia Shikuma as Site Leader and Ms. Debra Ogata-Arakaki as Site Coordinator (SC). Dr. Shikuma will have overall responsibility of site infrastructure, fiscal management and accountability for clinical trials operations. She will assume global responsibility to the Networks either personally or via designated Site Representatives for acceptable participant accrual and good clinical trials management. Ms. Ogata-Arakaki will manage the day to day clinical trials and regulatory operations of the site, and will supervise the performance of the research nursing/assistants and data management staff and assure that quality assurance is maintained for informed consent, patient enrollment and follow-up, patient confidentiality, toxicity management and data collection processes. She will coordinate the integration of clinic, laboratory and pharmacy.

Protocol management is the primary responsibility of the CRNs, a primary and a secondary (for backup), designated to oversee the recruitment efforts and coordinate the clinical management of each study. They function as patient care managers for all patients enrolled in their protocol. RAs are partnered with CRNs and are able to manage observational studies under the guidance of the CRNs. Recognizing the need to standardize program operations to maximize efficiency and reduce errors and problems, Standard Operating Procedures (SOP) were developed. Many of the program's clinical operations are guided by HACTU and DAIDS SOPs which provide a sound clinical research foundation. A list of HACTU SOPs is included in the Appendix.

Research subjects are seen in the Clint Spencer Clinic. A weekly evening clinic and a monthly Sat clinic are held. Individuals interested in participating in research are seen for an initial screening visit. If the patient elects to participate, the informed consent is signed (see Informed Consent SOP in the Appendix). All patients being considered for study participation are subsequently presented to the entire clinical research staff at weekly staff meeting for eligibility evaluation. Procedures are in place for meticulous screening and evaluation of potential research participants to avoid enrollment violations. This process has served our site well as we have never enrolled an ineligible patient. The CRNs are responsible for timely and accurate data transcription. One hundred % of all CRFs are reviewed by the DM prior to data entry for missing or errant data . The DM is responsible for monitoring the data entered into the main database and assisting the CRNs in reconciling discrepancies.

Six HACTU physician-investigators currently see research patients in clinic. It is the responsibility of the physician seeing the patient to insure that each patient in screening has understood his/her participating role and that all questions from the patient have been answered prior to entering the study. It is the policy of the Leahi site that all participants see a physician-researcher for each study visit with rare exceptions (such as for a simple blood draw). The participant's primary physician (PMD) is routinely provided

with a summary report after each study visit to relay any medical or study concerns from our program's research physician and safety labs from the visit. On study, it is the physician's responsibility to ensure that medical issues and abnormal laboratory values from that clinic visit are attended to until resolved. The PMD is notified in cases of urgent medical or study-related concerns. A physician researcher is available 24 hrs/day via a physician's exchange service in case of emergencies.

Weekly staff meetings are held with the clinical staff to review protocol, accrual, data management, quality assurance and staff issues and to coordinate the upcoming clinical, pharmacy and laboratory research patient needs. The physician-researchers join the meeting thereafter to discuss individual patient care problems, adverse events, and protocol issues. Any reportable adverse events are reported by the CRN to the DAIDS AE Office within the required guidelines (24-72 hr).

Our unit has a QA plan in place whose mission is to ensure production of high quality data. It is structured as a multi-tiered process with the primary QA being performed by the CRNs who review their own CRFs for accuracy and by the DM who checks for data omissions. Secondary QA is performed by a separate CRN or RA. A portion of all CRNs and RAs efforts are dedicated to QA performance activities. The QA audit focuses upon validating source documentation, clinical events, identification of toxicities and study endpoints and verifying that appropriate reporting has taken place. A QA committee meets quarterly to review and recommend solutions to problems in data quality identified by the committee. We take pride in the fact that the HACTU's excellent data production has been reflected by the consistently high quality performance evaluations by the external site monitors, Monthly Site Evaluation Reports, and Annual Site Performance Evaluations. An excerpt of the QA plan is included in the Appendix.

Laboratory Infrastructure: Blood and tissue collection, processing, packaging and shipment are performed by our site's Research Processing Laboratory located within the premises of the Clint Spencer Clinic. All collected specimens are entered into the ACTG-mandated LDMS computer system that tracks all ACTG specimens. Packaging and shipping is performed according to mandated ACTG, federal and state regulatory standards. Our processing laboratory meets all ACTG criteria for laboratory functions, and no regulatory citations have ever been received by our laboratory. Routine safety labs are done by Diagnostic Laboratory Services (DLS) Inc., a CLIA approved, CAP certified laboratory that provides service throughout the entire state of Hawaii. Although the CRNs and RAs perform a majority of the phlebotomy in the clinic, DLS has phlebotomy centers located on all major islands and is capable of performing all ACTG required safety tests. It is ACTG certified to perform basic CD4/CD8 and advanced flow cytometry.

Storage Facilities: Patient research charts are kept in files in the Leahi office that are locked at the close of each business day. The office itself is also locked. Files are stored or archived in locked storage cabinets on-site until notification from DAIDS that they can be destroyed. The specimen processing laboratory has adequate -80 freezers that are under double lock for storage of research specimens. The main repository of study drug is located in the Research Pharmacy at Queen's Medical Center (QMC) within locked rooms. The Research Pharmacy and Leahi Site are equipped with a -20 C refrigerator and -86 C freezer. Study drugs stored at QMC or at Leahi are maintained in temperature controlled environments in accordance with study drug requirements. Both Leahi and QMC have 24 hr back up generators, activated when power is compromised, therefore research specimens and study drug storage are appropriately maintained.

Pharmacy Management Plan: Pharmacy services are provided through a contractual agreement with Queen's Medical Center. This contract provides for repository space

within the Queen's Pharmacy for study medications, the services of our Site Pharmacist (S. Souza PharmD) and the services of a Pharmacy technician. Dr. Souza also provides extensive patient consultation and education. A Pharmacy Plan for Leahi is in place based on Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks (Sep 2002) that meets FDA regulations on the use of investigational drugs.

Dr. Souza provides oversight of all pharmacy needs for our site. A written, perpetual inventory record of study drug receipt, use, and disposition is kept that is separate from the records kept by the CRN for each individual patient. The Site Pharmacist or Alternate Pharmacist assures careful preparation and labeling of study medication, and dispenses the medication directly to the patient at QMC or to the CRN to be given to the patient at his/her study visit.

Dr. Souza is kept appraised of protocol status, amendments, safety information, and patient status, directly via email, Internet and weekly staff meetings. Our Research Site Pharmacy has an impeccable record of regulatory compliance and is committed to high quality standards consistent with Good Clinical Practice.

Training and Regulatory Compliance All new employees are instructed in patient confidentiality issues by Ms. Ogata-Arakaki, and the need for strict confidentiality continuously stressed to all staff. Clinical and laboratory staff are trained in protection of human subjects, OSHA regulations, universal precautions, shipping and transport of biohazardous material, HIPAA compliance, fire safety and occupational exposure procedures. Records of training in each of these categories are kept by our program. Laboratory staff are specifically trained in laboratory safety. Universal precautions are followed at all times. The appropriate equipment and supplies for universal precautions are available to the staff and patients in all clinic rooms and phlebotomy areas. An occupational exposure SOP, including one for HIV exposure detailing procedures for intervention, counseling and follow-up is in place. All clinicians are trained in Good Clinical Practice Guidelines and Health Insurance Portability and Accountability Act (HIPPA) requirements. Currently Ms. Ogata-Arakaki manages all IRB and regulatory functions including protocol and amendment submissions, and annual reports. She will continue to exercise oversight over the IRB processes. However, as she will also be assuming the role of Unit Coordinator for site operations both at Leahi and in Bangkok, plans are to hire a full time individual to assume IRB responsibilities at the Leahi site. The site has always been in good standing with the University IRB and the Protocol Registration Office and has maintained excellent regulatory compliance throughout its existence.

Plan for development of new investigators: The Leahi site takes seriously its training mission as an academic program. Internal medicine residents rotate through the Clint Spencer Clinic, and have opportunities to sign up for more intensive HIV care or research rotations. Summer undergraduate and medical student research opportunities are offered. This summer 6 undergraduates/medical students are conducting laboratory or clinical-based research within our program. Three researchers have completed an informal one year "HIV Fellowship" with our program. All currently remain in academic positions within JABSOM. Dr. Day is now Assistant Professor of Medicine and continues to work within our program. Dr. P Kuo is on sabbatical finishing this Immunology/Allergy fellowship and anticipated to return to work within our program in July of 2006. Dr. Imrie, a female junior investigator of Tongan ethnicity, a previous recipient of the AACTG Minority Training Grant, is currently Assistant Professor of Public Health Sciences and Epidemiology at JABSOM.

(iv) A.4. Site Contribution to Network and Priority Areas

This section describes the past and future protocol participation capabilities of this site. For potential scientific contribution capabilities, see section (ii).

Contribution to the HIV Vaccine Priority Area: As previously mentioned in section (ii) A, successful funding of the Hawaii Immunology and HIV Vaccine Core Activity expanded laboratory capabilities in HIV vaccine work and built institutional capacity for HIV vaccine trials work. Under the direction of Dr. J. Kim as Activity Leader for this Core, a NAb Lab (J. Kim), CD8 Lab (A. Imrie) and CD4 Lab (S. Ratto-Kim) were established. Local HIV demographics were assessed in preparation for clinical trials in HIV vaccines [59]. Based on this study, our assessment is that HIV vaccine trials in seronegative individuals are possible in Hawaii among the risk groups of men who have sex with men (MSM) and females of Asian Pacific Islander descent with other HIV risk factors. Leahi has extensive links to a community network capable of referring individuals at risk for HIV.

Leahi has in fact already demonstrated its ability to recruit and retain > 20 "high-risk" subjects/month on trial through its participation in the VaxGen "A Phase III Trial to Determine the Efficacy of Bivalent AIDSVAX B/B Vaccine in Adults at Risk of Sexually Transmitted HIV-1 Infection in North America and Europe" Trial. This study accrued 44 high-risk participants in Hawaii (42 unprotected MSM and two females with HIV+ partners). The ethnic breakdown of these participants were 75% Caucasians (33 pts), 14% Asian/Pacific Islander (6 pts), 7% Hispanic (3 pts) and 4% Other (2 pts). Despite study-mandated HIV prevention counseling performed during each study visit, seroconversion to HIV-positivity occurred in 6.8% (3 pts) during the 4 year period of study.

The HACTU processing laboratory capabilities as well as the specialized laboratory capabilities of the NAb Lab, CD8 Lab and CD4 Lab are available as needed for protocol participation. As previously mentioned the Neutralizing Antibody Laboratory run by Dr. J Kim has been supporting Nab needs of multiple projects nationally. The CD4 Laboratory run by Dr. S. Ratto-Kim provides lymphoproliferative assay support to 2 HACRP projects examining the relationship between loss of specific HIV T cell responses and activation/dysregulation of monocyte/macrophages and their role in HIV-associated dementia (HAD). The CD8 Laboratory run by Dr. Al. Imrie is supporting research to assess epitope specificity and ontogeny of HIV-specific blood and CSF CTL, as well as CTL responses to Dengue virus. We have the capabilities of collecting secretions and tissue samples from female and male genital tracts and this capability will be offered in support of HIV vaccine protocols.

Contribution to the AIDS Clinical Trials Group

Site Performance within the AACTG: HACTU has consistently met the rigorous clinical trials standard of the AACTG. In the last available annual site performance evaluation (7/1/03 to 6/30/04) [enclosed in the appendix with selected graphs], our site met the AACTG standards for relative cost per weighted accrual with a relative rank of 1.07 (standard: relative cost per weighted accrual $\leq$ 1.3 times the AACTG group median). For overall Data Performance, the Leahi site accrued 96.6 points and was rated as "outstanding" (standard $\geq$ 70 performance points; summary score rating: 95-100 outstanding; 85-94 very good; 70-84 satisfactory and <70 unsatisfactory). Our relative rate of voluntary discontinuation rate (# subjects withdrawn) in last year's AACTG evaluation (7/03-6/04) was 0.94 (goal: < 1.5 times the AACTG Group Median) and our relative rate of modified lost to follow-up rate (# subjects who have missed their last three study visits and no off-study form submitted) was 1.22 (standard: < 1.8 times the AACTG group median) [see graphs of selected Site Performance Areas in appendix]. By race/ethnicity (1991-6/17/05), 49.0% of HACTU's 986 participants were white not

Hispanic, 2.0% (20) black not Hispanic, 7.4% (73) Hispanic/Latino, 34.3% (338) Asian/ Pacific Islander, 2.5% (25) American/ Alaskan Native and 4.7% (46) not reported. It is significant that the 338 individuals of Asian/Pacific Islander ethnicity recruited by HACTU also represented 34% of ALL subjects of Asian/Pacific descent enrolled domestically since 1990 into Adult ACTG studies.

Researchers within our site have participated actively in key committees and focus groups of the AACTG and as chairs and co-investigators of protocols. *In the last evaluation, our site's scientific contribution was assessed as "no goal or standard but did well in comparison to the Group mean".* Members of our site participated as members in 35 national AACTG protocols, in 8 as chair or co-chairs of these protocols. A list of protocols with names and positions held in these protocols are summarized in the appendix. In terms of committee participation, members of our site have held/hold membership in the Executive Committee (C. Shikuma), the Site Evaluation Subcommittee (SES)(C. Shikuma), Treatment Strategies Research Agenda Committee [RAC] (J. Kim), the Complications of HIV RAC (C. Shikuma), Immune Based Therapy RAC (J. Kim, D. Ogata-Arakaki), Women's Committee (L. Kamemoto), Neurology Subcommittee (V. Valcour), Outcomes Committee (D. Chow), Resource Use & Cost Effectiveness Subcommittee (D. Chow), ACTG Genomics Focus Group (M. Gerschenson), Liver Subcommittee (M. Gerschenson), Mitochondrial Dysfunction Focus Group (C. Shikuma, M. Gerschenson), Cardiovascular Subcommittee (M. Gerschenson), Lab Technology Committee (P. Kondo), Site Operations Subcommittee (D. Ogata-Arakaki) and Site and Data Management Committee (D. Ogata-Arakaki).

Past and Future Contribution to the ACTG Network's Scientific Priority: Since 1990, the Leahi site has enrolled 985 participants into 120 AACTG clinical trials. Our site's operating philosophy has been to participate as broadly as possible in the AACTG's scientific agenda, based on site capability and applicability of the protocol to our patient population. Our past record of participation (full list of HACTU participation in AACTG trials enclosed in appendix) attests to the broadness of our participation. By priority areas listed by the ACTG Network, our past and proposed future "protocol" participation within the ACTG Network is as follows:

- Translational Research/Drug Development The Leahi site excels in the conduct of small intensive studies. HACTU is currently participating in protocols studying the use of β-D-2,6-Diaminopurine Dioxolane (DAPD) and Mycophenolate Mofetil (MMF) (A5165) and CCR5 inhibitor SCH 417690 (A5211) as anti-HIV compounds and in the use of MRK Ad5 HIV-1 gag vaccine (A5197) as adjunctive immunomodulator therapy to antiretroviral medications. In the future, HACTU plans to be fully involved in the translational research/drug development agenda to continue to test anti-HIV compounds as well as new therapies for co-infections (i.e. TB, HCV, malaria and HPV). Our seasoned clinical trials staff, centralized operations and committed group of patients that have supported our research are ideal for these smaller exploratory potentially high-impact studies.
- Optimization of Clinical Management and Co-Morbidities Our Leahi site has participated in all major antiretroviral trials sponsored by the AACTG designed to establish the best possible antiretroviral regimens for initiation in anti-retroviral naïve subjects (ACTG 175, 320, 384, 388, 5095, 5073,and 5203) and to optimize management of disease in antiretroviral experiences subjects (ACTG 359, 372,398, 5146). Our site has also participated in a broad range of co-morbidity trials from PCP (ACTG 108), Tuberculosis (ACTG 177, 222), Mycobacterium Avium Complex (MAC) disease (ACTG 196), Cytomegalovirus (CMV) (ACTG 360, A5030), HCV (ACTG 383, 5071, 5178), Kaposi's Sarcoma (ACTG 286), HAD (ACTG 736, 301, 5090), Oral Apthous Ulcers (ACTG 251), Cervical Dysplasia (ACTG 293), Papillomavirus (HPV) (A5029), wasting

(ACTG 892, 313, 329, 392) lipodystrophy (ACTG 5005s, 5079, 5082, 5110), dyslipidemias (A5087, A5186, 5209), carotid duplex (A5078), and osteoporosis (A5163).

Our Leahi site intends to continue our *broad-based* participation in optimization of clinical management and co-morbidities. We specifically intend to participate in all large scale antiretroviral trials intended for both HAART-naïve (A5202, EFV or ATV with RTV combined with FTC/TDF or ABC/3TC in naïve subjects; A5231 Efficacy of a Quadruple NRTI-based regimen vs. Standard of Care for Initial Rx) and experienced subjects (A5230, Study of LPV/r in Subjects with Virologic Relapse on NNRTI-Containing Regimens; A5212 rHU Keratinocyte Growth Factor for Inadequate CD4 Recovery). In the area of co-morbidities, we will continue our tradition of opening studies of HCV co-infection (A 5184 ART impact on PEG IFN Alfa-2A + Ribavirin for HCV in HCV/HIV co-infection w/high CD4; A5204 High dose PEG-IFN + Ribavirin for HCV Genotype 1 in HIV Co-Infection and Mono-infection; A5232 Optimizing Vaccine Response in HIV-1, HCV and co-infected subjects) and HBV co-infection (A5220 Response to HBV Vaccine with GM-CSF as a vaccine adjuvant). Our expertise and capabilities in the field of HIV gynecology will enable us to participate fully in current (A5188 PK Study of Transdermal & Oral Contraceptive in HIV-1 Women on LPV/r) and future studies related to women's issues. Expertise within our site will also allow us to fully participate in current and future studies in the field of mitochondrial/metabolic co-morbidities (A5209 Safety, Efficacy, Tolerability of Ezetimibe with Statin Therapy for Elevated LDL Cholesterol; A5229 Uridine supplementation in HIV lipoatrophy) and in the NeuroAIDS field (A5157 Acetyl L Carnitine for Dideoxynucleoside Associated Distal Peripheral Neuropathy).

- Vaccine Research and Development Our Leahi site intends to assist in the ACTG's aims to evaluate the immunogenicity and safety of selected candidate HIV-1 vaccines in the HIV-1 infected population and to determine the correlates of immunologic control of viral replication. Our Leahi site is currently participating in A5197 Antiretroviral Effect of MRK Ad5 HIV- 1 Gag Vaccine in HIV Individuals Stopping ART. Future participation is planned in A5176 Tolerability, safety, and immunogenicity of LC002 (Derma Vir vaccine); A5220 Response to HBV Vaccine with GM-CSF as a vaccine adjuvant; and A5193 Safety/Immunogenicity of SQ MVA-mBN32 HIV-1 Vaccine & MVA-BN.
- Prevention of Mother-to-Child Transmission of HIV As possible, HACTU will participate in ACTG's aims to provide for optimal safety of women who undergo antiretroviral therapy as part of efforts to prevent mother-to-child transmission of HIV. While Hawaii does not have a large number of pregnant HIV-infected women (averaging approximately 5 pregnancies/year in the entire state), Dr. Kamemoto, our Ob/Gyn specialist, either personally delivers or has been consulted on almost all deliveries of HIV+ women in Hawaii over the past 5 years. This has allowed the Leahi site to recruit 2 of 105 subjects nationally enrolled in A5084 Evaluation of Metabolic Complications associated with Antiretroviral Medications in HIV-1-infected Pregnant Women.
- Prevention of HIV-1 In this priority area, ACTG aims to develop approaches to identify, recruit and retain individuals who are acutely infected with HIV-1, evaluate the impact of ARV and other interventions on HIV transmission and to evaluate biological markers and its correlation with HIV transmission and/or acquisition. Our Leahi site enrolled 6 of 121 subjects enrolled nationally into ACTG 371, a trial of ARV intervention for subjects seroconverting or in early infection. The proposed HACTU scientific agenda that now includes studies of HIV vaccines/microbicides in HIV seronegative individuals, access to the growing HIV clinic population within our own Clint Spencer Clinic, and our close relationship with community HIV resources should facilitate successful participation in this priority area.
- Oral HIV/AIDS Research Alliance The ACTG Leadership Network intends to

form an infrastructure capable of conducting research on the pathogenesis and therapy of oral manifestations of HIV infection. To allow Leahi site participation in this exciting new area of HIV research, support has been solicited from Dr. L. Kagihara, Associate Professor and JABSOM's new Director of Oral Health and Research. She is prepared to participate scientifically as well as assist in protocol mandated procedures dealing with oral health.

Contribution to the Microbicides Priority Area

Although HACTU has never participated in microbicide trials, HACTU has participated in several NIH trials that involved genital tract collection studies within the AACTG (ACTG 293, 701, 866,880, A5029) and the Women's Interagency HIV Study. We have also participated in a male genital tract collection study (ACTG 701). Dr. Kamemoto is well-qualified to collect samples from the female and male genital tract, as well as anal biopsies and washes for the assessment of mucosal immune factors. In addition to our Obstetrician/Gynecologist, our staff/resources includes a women's health nurse practitioner, C. Milne, who also collects female genital tract specimens and an STD specialist (A Katz).

(iv) A.5 Recruitment and Retention

Recruitment Strategies (including scaling up recruitment to >100 participants on study/month)

Recruitment of HIV Participants: Our current patient census far exceeds the mandatory 20 patients on study/month required by this RFA. Our average annual accrual on AACTG studies (Jan 1993 [when the site was fully functional] to Dec, 2004) was 66 patients/year and it is estimated therefore that we ran an average census of approximately 100 participants on study/month. In recent years this has dropped to an estimated 60-80 participants on study/month secondary to the complexity and narrow entry criteria of the ACTG studies involved. Enrollment is highly dependent on the entry criteria of each study. However, should a need to conduct a large-scale study in HIV+ subjects become necessary due to an exciting new treatment alternative, scaling up to 100 participants on study/month should be possible. Traditionally, the largest number of referrals for therapeutic trials have come from community referral. We anticipate that this will continue. Several unique recruitment tools are used with success by our program: ▪ Bimonthly, a "pink sheet" [sample enclosed in appendix] is generated detailing research studies open for enrollment and distributed widely at various functions and mailed extensively, utilizing a mailing sheet generated by our program of key referral sources. HACRP also maintains a website at http://www.hawaii.edu/hacrp/ which includes a list of enrolling studies. ▪ The Hawaii Seropositivity and Medical Management [HSPAMM] Program is a state program created to encourage HIV-infected persons to seek medical care, provide regular clinical monitoring for HIV-infected persons in all stages of HIV illness, establish an anonymous database to track the natural history of HIV in Hawaii and to assist in HIV research activities. HSPAMM works through a statewide network of physicians who provide primary health care to HIV-infected patients and recruit patients for participation in the program. HSPAMM provides 2 evaluations/year which include a patient self-administered questionnaire (demographics, HIV risk factors, and clinical history), a physician assessment (HIV clinical manifestations, current medications, and a physical examination), and a standard laboratory panel which includes routine tests as well as HBV and HCV serologies, CD4, and Roche HIV RNA. As of May 31, 2005, 238 physicians statewide have enrolled a total of 2,906 patients of whom 856 are active. The HSPAMM database allows targeted screening for protocol eligibility by database criteria and is utilized routinely by our program for this purpose. While the database operates by ID numbers, individuals identified as potentially eligible for study can be

accessed via their primary health care providers who make the initial contact for our program. ▪ Approximately 250 of the roughly 500 participants in the Hawaii Aging with HIV Cohort (Memory) study, run by HACRP's Office of Neurology and Aging Research [ONAR], are HIV seropositive. Participants, as they are seen for their annual visit to this Memory study, are discussed in Friday staff meeting. If other studies that may be appropriate for the participants are found, the ONAR staff initiate the patient contact to query for their interest in screening for that particular study.

Recruitment of HIV Seronegative "Low-Risk" and "High-Risk" Participants Our program has established ties with community organizations working with both HIV-infected people as well as those at high risk of contracting HIV. This includes the Hawaii State STD Branch, Diamond Head STD Clinic, 4 AIDS Service Organizations (ASOs), 2 Drug Assistance Programs, several community clinics, and a Gay and Lesbian Community Center. These organizations, currently steady sources of referrals for our AACTG studies, have now committed themselves to assist us in recruiting for vaccine and microbicide research within the high risk HIV-negative populations they serve. Letters from these organizations are included in the appendix of this application. In particular the ASOs [The Life Foundation (Oahu), Hawaii Island HIV/AIDS Foundation (Hawaii), Maui AIDS Foundation (Maui and Molokai) and Malama Pono (Kauai)] have active outreach and education programs targeting the general population and groups at high risk of HIV infection. They are well integrated into the communities and their staff reflect the ethnic, sexual and gender orientation of the communities they seek to serve. Groups specifically targeted include native Hawaiians and Pacific Islanders, MSM, trans-gendered individuals and women and youth. Collectively it is estimated that the ASOs conduct over 26,000 prevention interventions a year, the majority of these being individual outreach contacts rather than group education.

It is anticipated that the majority (>75%) of high risk participants will come from Oahu. We plan to therefore work closely with the Life Foundation which has extensive community contacts and several established programs with minority ethnic groups of interest and groups of particular risk on Oahu. A plan has been agreed upon to station an HACTU staff member within the Life Foundation prevention program to work closely with their staff and develop relationships within the community. Having this arrangement in place will allow us to scale up quickly should a need arise to scale up to >100 required participants. Additional assistance has been solicited from the Community Health Outreach Work to Prevent AIDS (CHOW) and the Drug Assistance Services of Hawaii (DASH) both of whom work with large populations of injection drug users and have a specific focus on HIV prevention. CHOW has an extensive outreach program which exchanged 424,166 needles in 2004 and DASH is the largest treatment program in Hawaii, serving 370 patients at any given time. These programs have committed to helping us recruit within the injection drug using population should a study call for this group. The Gay and Lesbian Community Center is a Statewide organization which coordinates, facilitates and develops lesbian, gay, bisexual, trans-gendered and questioning groups and creates bridges to the community at large. They are the most established and largest gay organization in Hawaii and reach a large proportion of the gay population through events, newsletters and their website.

It is anticipated that the recruitment of individuals of Native Hawaiian ethnicity and specifically of high risk HIV seronegative women for vaccines or microbicide studies will be enhanced by specific assistance from public health centers, clinic and programs that deal with this population. Support has been specifically obtained from the Waianae Coast Comprehensive Health Center which provides services for 21,000 clients/year of which 50% are Native Hawaiians and 25% are Asian and from the Kapiolani Women's

Health Clinic that provides 650-750 patients visits/month, more than half of whom are women of Asian or Pacific Islander descent. A letter of support has been obtained from Dr. M. Mau, head of JABSOM's Department of Native Hawaiian Health promising specific introduction to Community organizations serving Native Hawaiian communities should this be deemed important in the future for recruitment purposes.

Our CRNs/RA regularly attend functions such as the Life Foundation weekly lunches provided to their infected clients and People with AIDS food basket, to present their studies and mingle with the attendees.

Retention Strategies

The Leahi site has traditionally performed well in the retention of research participants. Individualized and personalized care provided by the CRNs is perhaps the most crucial key to retention. The nurses have instituted measures to increase the comfort levels of our patients as they come for their research visits. Food and drinks are provided for patients particularly for those who must come fasting for their research visits. As side-effects of medications are a major factor in poor retention, it is the established practice of HACTU not only to review potential side effects and instruct patients to call if problems arise but to establish phone contact within the first week and on an on-going basis to insure that the patient is tolerating study medications. Patient transportation to HIV Research Clinic (taxi service, bus pass, reimbursement for gasoline, airline travel from neighbor islands) is provided as warranted. Hotel accommodation for an overnight stay on Oahu is arranged for research participants requiring extended visits (such as PK studies). Money for childcare is provided as warranted. For women who need to bring their small children, one of the exam rooms at Leahi is also equipped with a small play area. Our program also believes in assisting as possible with medical and case management needs of our research participants. Calls to their PMDs relaying our suggestions (i.e. ARV regimen recommendations in cases of virologic failure) or assistance in linking the participants with case management services at the various AIDS service organizations or with substance abuse services have been appreciated by our participants and enhance our retention efforts. For the few patients with difficulty in English, language interpretation services are available to our program from QMC and Kapiolani Medical Center for Women and Children.

Plans to Increase Clinical Trials Infrastructure to Accommodate 100 Study Participants/month

The Leahi site has the luxury of operating within a close group of investigators and their clinical/laboratory staff within HACRP who have shared personnel resources to meet the demands of all projects performed under HACRP. Funded projects within HACRP in addition to our AACTG grant which requires clinical research resource includes our "Hawaii Aging with HIV" cohort study, EXPORT Lipoatrophy Study, ATP Production in Lipoatrophy Study, Autonomic Dysfunction in HIV Study, Role of Macrophage in HIV Dementia Study, Role of Exercise in HIV Study, and Sleep in HIV Study. This has brought economy of scale while at the same time allowing HACRP maximum maneuverability to conduct clinical trials. HACRP, in total has access to 5 CRNs and 5 CRAs. While plans to increase capacity to 100 study participants/month may ultimately require the hire of more clinical staff, the shared clinical resources of HACRP will allow immediate pulling of some HACRP resources into the study to initiate the study. Finally, JABSOM has a RCMI-based Clinical Research Center (CRC) funded by NCRR. We have utilized their services in the past for extended PK studies and request for clinical staff support is possible. Their openness to consider this possibility is supported in a letter from Dr. David Easa, their Director, which is included with this application.

(iv) A.6. Plan for Community Involvement

Community Advisory Board (CAB) Established in November of 1990, Leahi's CAB is unique in that it also serves to advise the Hawaii State STD Branch's programs providing clinical lab, drug and insurance assistance to the HIV infected community (HSPAMM, Hawaii Drug Assistance Program [HDAP] and Hawaii COBRA [HCOBRA] Program; more information at http://mano.icsd.hawaii.gov/health/healthy-lifestyles/std-aids/hspamm.html). This arose out of the common developmental history of these university and state programs and has functioned well to link these resources to meet the needs of the HIV community. Leahi's CAB follows the guidelines mandated by the AACTG (http://aactg.s-3.com/pub/docs/cabguide.htm). Sean Hannah, a HIV+ community member from Hilo on the Big Island currently serves as CAB chair and Melissa Castillo from our program provides administrative support for its functions. CAB functions include protocol review, outreach/recruitment, community input on research prioritization, identifying barriers to research participation by minorities and liaison with the Community Constituency Group (CCG) of the AACTG. The CAB currently has 16 members including membership of HIV+ females and individuals of API ethnic descent. CAB meetings are held on a monthly schedule. Airfare is provided to enable the members from the 3 main neighbor islands to send representatives to the monthly meetings on Oahu. HACTU has made a commitment to the CAB to have a HACTU leadership representative [usually the PI] at each CAB meeting to discuss new studies, answer questions and concerns regarding its research operations and to be available for discussion of HACTU research priorities. Research nurses also attend the meetings particularly when their studies are first opening for enrollment to answer protocol questions. The meetings are also usually attended by Mr. Peter Whiticar, Director of the Hawaii State STD Division.

Scientific Advisory Board (SAB) The SAB is an advisory board composed of community physicians and other community leaders active in HIV care. Similar to the CAB, the SAB advises the HSPAMM/HDAP/HCOBRA state programs as well and also convenes monthly. The SAB advises on the overall direction of the site's research, discusses the feasibility and appropriateness of each protocol for Hawaii's HIV- infected community, assists in recruitment of participants and monitors the list of open protocols. Dr. Shikuma and other research physicians from our program routinely attend the SAB meetings. It is estimated that the community physicians on the SAB care for >75% of the HIV+ population who are in care on Oahu. This includes Dr. Cyril Goshima, a community physician in private practice with the largest panel of HIV+ patients in Honolulu who also heads the AIDS Education Project for UH, Dr. Drew Kovach representing the Kaiser Permanente's (estimated to be responsible for health insurance for 25% of the overall population in Hawaii) HIV Clinic, and Dr. Ace Johnson representing the Veterans Administration's HIV clinic. A letter of support signed by members of our SAB is included with this application.

Community Outreach Research done in any community must operate with the consent and buy-in of the larger community that it serves. Brought into existence originally in 1990 with the strong support of community physicians and community/State HIV programs who believed in the value of research for their HIV infected patients, our university-based research program serves and works as part of this community. Quarterly newsletters from HACRP edited by V. Valcour M.D. is widely distributed to the community and contain health topics of interest to the community such as exercise, neurocognitive dysfunction and anal dysplasia. In collaboration with the AIDS Education Project, our faculty recently presented a "Discoveries from the Hawaii AIDS Clinical Trials" series to HIV community audiences on Oahu, Kauai, Maui and the Big Island.

Our physician-researchers are routinely accessed by community physicians for telephone or formal medical consultations on complex HIV cases. Our program is utilized as a resource in identifying appropriate physicians or other medical services for clients of the various ASOs. All patients regardless of insurance status are seen in our Clint Spencer Clinic. Our program's physicians alert the research patient's primary physician to medical problems discovered as part of the research patient's study visit, and often play a role in assisting with the appropriate resolution of these problems. Within the past year, our faculty presented "Update from the 12th CROI" and "New Discoveries" lectures to HIV treating physicians, and gave grand rounds at UH Dept Med, VA, Pali Momi and St. Francis Medical Centers. Attempts have been made to work together to maximize resources for our patients. Examples include on-site social services to the Clint Spencer Clinic provided by our Honolulu ASO (Life Foundation), and the joint HACRP-AIDS Education Project plans for training of Vietnamese military physicians in HIV management anticipated in Honolulu this year as part of the Vietnamese PEPFAR.

(iv) B. BANGKOK Clinical Research Site

(iv) B.1 Description of the Clinical Research Site

Description of the Site Environment and Patient Catchment Area

Thailand and the City of Bangkok: The Kingdom of Thailand is a country in Southeast Asia bordering Laos and Cambodia to the east, the Gulf of Thailand and Malaysia to the south, and the Andaman Sea and Myanmar to the west. The total population is approximately 64 million, the majority of whom are ethnic Thai and Lao. Other ethnic groups include Thai Chinese, Malays, Mon, Khmer and various indigenous hill tribes. Around 95% of Thais are Buddhists and the national language, which is written in its own alphabet, is Thai. The median age is 30 years, and 70% of its population is in the 15-64 year age group. The infant mortality rate is 20.5 deaths/1,000 live births, life expectancy is 72 years and literacy rate is 93%. Per capita GDP is $8,100, compared with its neighbors Burma with a per capita GDP of $1700, Laos $1900 and Cambodia $2000.

The capital, Bangkok, lies in south-central Thailand and has a population of approximately 5.7 million, while another 9.4 million people live in the greater metropolitan area. Bangkok is the cultural, political, and industrial heart of Thailand and regional center of trade, economy and biomedical research.

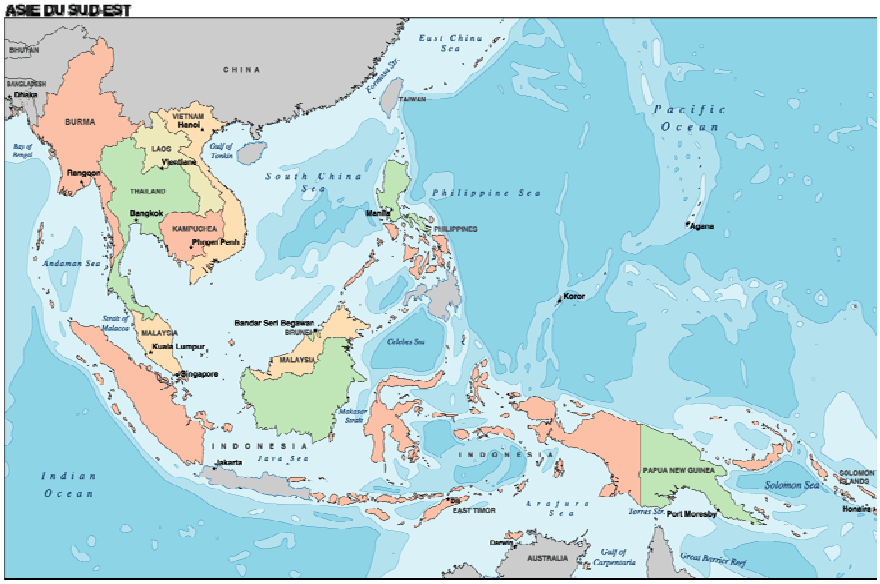


Figure 6. Bangkok in the heart of Southeast Asia

HIV/AIDS in Thailand: Thailand was hit early by the AIDS epidemic and despite aggressive intervention to curb disease, the prevalence of HIV exceeds 1% [60]. An estimated 1 million Thais are infected. About half of these individuals have died and more than 35,000 children have been orphaned. Individuals between the ages of 25 and 35, in their peak years of

productivity, make up over half of the reported cases of HIV/AIDS. The reported male to female ratio is 2.7:1. According to the Thai Ministry of Public Health (MOPH) nearly 20,000 new infections are expected annually despite aggressive public health interventions. Based on HIV seroprevalence data from Royal Thai Army conscripts and from antenatal clinics, there may be 75,000 – 94,000 persons between the ages of 20 – 30 who are infected with HIV-1 in Bangkok.

The first case of AIDS in Thailand was reported in 1984. HIV infection in Thailand began in the homosexual population and quickly spread to intravenous drug use (IDU) population in the late 1980s, and then to sex workers (SW). Because an estimated 22% of adult men visited sex workers, the epidemic then spread to the general population, putting monogamous spouses of infected men at risk. The Thai government implemented its "100% condom use in commercial sex programme", and HIV prevalence in the general population fell with a decline in prevalent HIV infection among military recruits from 4% in 1993 to 0.5% in 2001 [61], and among pregnant women from 2.4% in 1995 to 1.2% in 2003.

Despite these successes, HIV may be spreading in other at-risk populations in Thailand. Injection drug use appears to be re-emerging as an important risk behavior maintaining endemic HIV transmission in Thailand. In a study of HIV infection prevalence and risk behaviors among eight cohorts of 21 year-old randomly selected male military conscripts in northern Thailand, the rate of reported history of illicit drug use rose from 1% in1991 to 4.2% in1997 [62]. Among men found to be positive for HIV, those with a history of drug use increased from 1.0% in 1991 to 25.8% in 1998. Since HCV shares parenteral transmission as a route of infection, the high HCV seropositivity (50.7%) among HIV infected men identified at screening for HIV vaccine trials lends further evidence of IDU as an major risk factor for HIV transmission in Thailand [63].

Concern is also growing regarding the rates of HIV infection among Thailand's MSM population. In a recent cross-sectional analysis, venue-day-time sampling found a startling 17.3% prevalence of HIV in MSM in Bangkok [64]. Since research among young Thai males has demonstrated varying percentages (3.3% to 16.0%) of men reporting same-sex experiences, there is a possibility that the number of MSM in Thailand may be quite large [62, 65-67].

Thailand has made a concerted effort to reach a goal of universal access to antiretroviral drugs for those in need. The country has a national health care system with universal access to medical care enhanced in 2001 by the Thai government's introduction of the "30 Baht Program" (40 baht = 1 US dollar). This program of comprehensive medical care was recently expanded to cover the costs of HIV care with minimal (30 Baht) co-payment per visit. Since 2003, Thailand produces generic antiretroviral drugs to provide a fixed combination formulation of stavudine, lamivudine and nevirapine (GPOVir) as an initial regimen for infected Thais. The development and manufacture of generics has been accompanied in Thailand by a good quality assurance program developed by the Thai TRCARC/HIV-NAT collaboration. A national program for HIV patients to have access to antiretroviral therapy called "NAPHA" began in 2003 with a goal of eventually covering 50,000 patients.

There are differences between Southeast Asia and Western countries in both the molecular epidemiology and the natural history of HIV/AIDS. The circulating recombinant form CRF01_AE of the HIV-1 virus predominates in Thailand [60]. Progression from HIV infection to AIDS may be faster than in the West: 6.9 years in a Thai cohort [68] compared with 10 years or more in most pre-HAART western cohorts [69]. Whether host immune responses or viral characteristics account for these differences is unclear. The three most common opportunistic infections are tuberculosis

(mostly extra-pulmonary), cryptococcosis and Pneumocystis carinii pneumonia [60]. Disseminated Penicillium marneffei occurs with some frequency in northern Thailand [60]. Up to 30% of HIV+ patients with chronic fever or weight loss in Thailand were found to be positive for MAC disease [70].

Description of the Organizations involved in this Collaboration

Armed Forces Research Institute of the Medical Sciences (AFRIMS) The Armed Forces Research Institute of Medical Sciences (AFRIMS) operates as a joint United States-Thai military research venture, and has a combined staff of over 300 US and Thai military and civilians from both countries. The Commander of AFRIMS is a Thai Army Officer (currently Major General (Dr.) Suebpong Sangkharomya). The U.S. Component has a U.S. Army officer in command (COL Carl Mason). Letters of collaboration are attached. The U.S. component functions as a special foreign activity of the Walter Reed Army Institute of Research (WRAIR) in Washington, D.C. and of the U.S. Army Medical Research and Materiel Command. AFRIMS has the largest medical library in Southeast Asia and a modern research animal facility that is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC). In 2001, the U.S. Institute of Medicine called AFRIMS "probably the most sophisticated diagnostic and research laboratory in all of Southeast Asia."

The US component of AFRIMS conducts collaborative research on tropical infectious diseases of military and public health importance. US-AFRIMS is involved in vaccine development and testing with areas of expertise ranging from the isolation of new etiologic agents to the field-testing of new vaccines. Vaccines for dysentery, dengue fever, hepatitis E and HIV currently are under development at AFRIMS. Products originally field tested or developed at AFRIMS include Hepatitis A vaccine, Japanese Encephalitis Vaccine, and several compounds for the prevention and treatment of malaria. The Department of Retrovirology conducts phase I-III trials of preventive HIV vaccines for use in U.S. military members deployed to HIV endemic areas outside the United States. In collaboration with the Thai Ministry of Public Health, this Department currently assists in management of a phase III HIV vaccine trial to assess the "prime-boost" strategy using ALVAC-HIV (vCP1521) and AIDSVAX B/E in 16,000 young HIV-negative Thai adults. The Dept of Retrovirology is directed by LTC Jerome Kim M.D. who also holds an appointment as Associate Professor of Medicine at University of Hawaii.

The Thai component of AFRIMS, falls under the Royal Thai Army (RTA) Medical Department and has a long reputation as the military's premier biomedical research institution in Thailand. The Division of Research is one of three divisions and conducts clinical, epidemiological and laboratory studies of infectious diseases including HIV/AIDS. As previously mentioned, the Royal Thai Army Clinical Research Center AFRIMS (RTACRC AFRIMS) is utilized for AFRIMS's HIV vaccine research needs and is the clinic facility proposed for the HACTU-Bangkok site.

The Department of Retrovirology laboratory occupies 2,600 sq. ft. on the 7th floor of the Main Building at AFRIMS, adjacent to PMK. This laboratory currently provides support for HACRP's on-going NeuroAIDS study and will provide the necessary specimen processing and shipment function for the HACTU-Bangkok site. The HIV Clinical Research Laboratory, under Dr. Mark de Souza, is part of the Department of Retrovirology and is considered one of the premier overseas HIV laboratories for the evaluation of immune responses induced by HIV vaccines and in studies of HIV infected Thais [1, 4-6, 71-75]. The laboratory is used as a training platform for African HIV vaccine laboratory efforts, and Dr. de Souza is now actively involved in the CAP certification of laboratories in 5 African nations. From the standpoint of outstanding

specimen processing, archiving and shipping to the development and validation of novel techniques for the evaluation of CD8 or CD4 T cell responses, the inclusion of the HIV Clinical Research Laboratory is one of the key components of this application. While many sites can conduct clinical trials according to Good Clinical Practices, the Bangkok site of this application can also assure adequate specimen processing, clinical laboratory back-up and the ability to perform advanced, validated assays in a strict, controlled environment, aspects that are critical to a study's successful completion. The AFRIMS laboratory has received its second CAP certification in 2004. In October of 2005, clinical chemistry and HIV resistance testing will be added to the list of certified clinical tests. DAIDS reviewed and approved the laboratory prior to the initiation of the Phase III clinical trial and continuous monitoring of SOPs and laboratory execution has been provided by Quintiles under contract with the U.S. Army. A standing QA committee meets regularly and addresses needs and concerns. The laboratory has been reviewed for compliance with 21CFR11 and was found to be in compliance for the Phase III trial. In the current Phase III trial, less than 1% of samples were processed more than 4 hours after being drawn; this despite a study area that encompasses two provinces in a developing country.

The laboratory has a tremendous capacity for the performance of advanced immunological studies on site. Using protocols and SOPs developed by the Division of Retrovirology in conjunction with the HIV Vaccine Trials Network (HVTN), the laboratory performed on site over 1000 chromium release CTL assays. In addition, the laboratory has experience with ELISpot (performed on the same samples) and with flow cytometric detection of IL-2 and IFN-gamma in CD8 (and CD4+) T cells. It should be noted that the networks under Partnership for AIDS Vaccine Evaluation (PAVE) are still in the process of standardizing the assay described above; the AFRIMS assay is developed in conjunction with studies from Dr. Josephine Cox. Dr. S. Ratto Kim (also UH faculty), has published extensively in the analysis of CD4 helper cell responses to HIV vaccines and is leading this effort in conjunction with Dr. deSouza. Additional SOPs using CCR7 and CD107 are being evaluated. This Lab also has experience as well with both antibody dependent cellular cytotoxicity (ADCC) and natural killer (NK) cell activity in HIV vaccine recipients and HIV infected Thais.

Phramongkutklao Hospital (PMK) and School of Medicine: PMK hospital and medical center is located immediately adjacent to AFRIMS. PMK is the main referral hospital of the Thai Royal Army Medical Department with an inpatient census of 26,188 and an outpatient census of 942,808 visits in 2004. PMK also has extension clinics serving several predominantly disadvantaged neighborhoods of Bangkok with 82,884 patient visits in 2004. The public health system in Thailand allows its citizens freedom to access any public medical hospital system, regardless of military affiliation. Consequently, 648,654 of the OPD visits (68.6%) to PMK during 2004 were by civilians. PMK is also the main teaching hospital of the Phramongkutklao School of Medicine and offers both residency and subspecialty training programs. Research is encouraged; house staff in most of the post-graduate training programs must complete at least one research project to become board-eligible. The PMK College of Medicine was established in 1975 and is the sole uniformed services medical college in Thailand. .

The ID outpatient clinic is located on the 3rd floor of the PMK outpatient building. This clinic currently provides care for approximately 500 HIV infected patients. Three senior full time ID-trained physicians and 2-3 residents staff the clinic. An ID fellow is scheduled to begin work with the ID service at PMK later this year. The Chief of Service, Dr. Sataporn Thitvichianlert, has experience in antiretroviral management and has participated in several antiretroviral drug trials. Statistics on the HIV-infected patients

kept by the ID Clinic reveals that the male to female ratio is 1.5:1; heterosexual transmission accounts for 87% of cases, with MSM (10%) and IVDU (3%) risks being less frequent. Approximately 5% of couples in this patient population are discordant. About 10% of patients are co-infected with HBV and 3% with HCV.
During the past year, approximately 150 new adult HIV cases presented to the ID clinic. The majority of cases presented with AIDS-defining illnesses. Thirty (20 %) of these patients had TB, 20 (13%) had PCP, and 15 (19%) had cryptococcal meningitis. Nearly 95% of HIV-infected individuals at PMK receive HAART, with the vast majority of these (90%) receiving a 2NRTI plus NNRTI regimen. Immune reconstitution inflammatory syndrome (IRIS) is quite common in their patient population, occurring in around 10% of HAART-treated individuals. Most of these patients present late in the course of their HIV-infection and have low CD4 counts when first seen.

The Thai Red Cross AIDS Research Centre (TRCARC) and the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) TRCARC was established in 1987 to coordinate the HIV prevention and treatment activities of the Thai Red Cross Society. These include the prevention of mother to child transmission (MTCT) project, the Columbia University MTCT Plus Program and the anonymous Voluntary Counseling and Testing (VCT) clinic. Opened in 1991, this clinic is visited by approximately 800 clients per month and provides VCT in addition to CD4 and viral load testing, screening for tuberculosis and a women's health clinic.

HIV-NAT is a part of the TRCARC that devotes its effort to HIV clinical research. HIV-NAT is well recognized for its expertise in HIV clinical trials. Since its establishment in 1996, there have been 1800 patients enrolled in 56 studies. There are currently 27 ongoing trials including the following: Esprit, SMART, STALWART, and CIPRA. Studies at HIV-NAT evaluate efficacy of ARV regimens, treatment of opportunistic infections, and strategies for hepatitis B/C co-infection, ARV toxicity especially lipodystrophy and mitochondrial toxicity, structured treatment interruption and ARV resistance. HIV-NAT has 78 full time staff with 7 doctors, 15 study nurses, 7 monitors, 3 statisticians, 2 data managers, 3 data entry personnel, 2 pharmacists, 3 assistant pharmacists, 12 laboratory technicians and other administrative staff.

University of Hawaii (UH) Training and Research Interests at the Bangkok site HACRP's existing clinical research infrastructure at PMK/AFRIMS support UHM's role in several HIV training and research initiatives. HACRP is an invited partner in the U.S. military's Joint Asia-Pacific HIV/AIDS Prevention Program. The key objective of this program is to provide "military to military" assistance in developing effective HIV prevention and treatment programs within SE Asia foreign militaries. Beginning in late 2003, a series of workshops have been held ranging in topic from strategic planning for HIV/AIDS Policy within the military, HIV counseling, HIV diagnostics, and HIV care/management. Attendees to these workshops have come from more than 8 Southeast Asia countries. While some of these workshops have been held as within country workshops, most have been held at AFRIMS in Bangkok, Thailand, utilizing PMK classroom space. The central location of Bangkok within Asia simplifies travel logistics for participants coming from various countries in Southeast Asia. In addition, the established US–Thai AFRIMS collaboration and access to the expertise of the Retrovirology Lab at AFRIMS facilitate logistical issues of securing appropriate auditorium, classroom, teaching expertise and administrative support. UH faculty (Drs Shikuma, Kamemoto, Marten, Goshima, Kim, and Souza) have participated in various HIV/AIDS workshops, in particular, assisting with the HIV care and management lectures needed for these workshops.

UH is a partner with the COE to meet the objectives of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) for Vietnam. PEPFAR is a US, 5 year, $15

billion global initiative to combat the HIV/AIDS epidemic in 15 countries most severely affected by the HIV/AIDS epidemic. With a strong emphasis on providing treatment, including the distribution of ARV drugs, the specific goal for HACRP's role in the Vietnam PEPFAR is to assist in the training of Vietnamese military physicians in HIV/AIDS management and to provide expertise for the establishment of effective HIV care clinics within their military. HACRP will conduct intensive HIV/AIDS care and management training sessions for 6 Vietnamese military physicians this year. While ARV therapy will be taught in Honolulu, it was felt more appropriate to conduct training in opportunistic infection (OI) management in Bangkok where a high incidence of OIs continue to be seen. This aspect of the training will be overseen by Dr. J. Ananworanich as a UH faculty member.

Funding from the Gilead Foundation will extend UH's HIV training mission to include civilian physicians from various Southeast Asian countries. This particular initiative will partner not only with AFRIMS and PMK but also with the Thai Ministry of Health (MOPH) and Bamrasnaradura Institute, a 650-bed specialty hospital dedicated to Infectious Diseases and operated by MOPH. Widely known in Thailand as "the HIV hospital", Bamrasnaradura Institute provided HIV care for 48,780 outpatients and 2,495 inpatients in 2003.

The working relationships established at AFRIMS and PMK were leveraged to extend HACRP's capacity to conduct clinical research studies in Thailand . The current international dementia study at PMK (UH-PMK NeuroAIDS Study 001:Predictors of Neurocognitive Decline and Survival in HIV-infected Subjects) is a collaborative research project between Dr. Valcour from HACRP, PMK Neurologists (Dr. Nidhinandana and Sithinamsuwan) and a PMK ID Specialist (Dr. Thitvichianlert). Originally designed as a cross-sectional study with limited follow-up, this study is now funded as a longitudinal cohort [R21MH072388-01, PI V Valcour, "Macrophages, HAART and HIV Dementia in Thailand]. The project enrolls ARV naïve HIV-infected subjects with HAD just prior to beginning ARV. There are two control groups: AIDS subjects without HAD just prior to beginning ARV and HIV seronegative controls. Patients are seen at the clinic facilities of the RTACRC AFRIMS. .

The specific aims of the longitudinal study is to assess the relationship between monocyte/macrophage activation and dementia in ARV naïve patients living in Thailand and to determine novel secretory products of monocyte/macrophages through proteonomics-based technology in collaboration with the University of California [UCSF (L. Pulliam)]. Flow cytometry, viable separation and storage of PBMC, and processing of sera and plasma are conducted by the AFRIMS Dept Retrovirology HIV Clinical Research Lab. The study has now accrued 36 of the target 45 cases evenly divided among study groups and preliminary findings were reported at an international conference in Frascati, Italy in June 2005.

The UH HIV training and research base at Bangkok now consists of 5 UH faculty members in Bangkok (G. Watt, J. Kim, S. Ratto-Kim and 2 newly appointed faculty members J. Ananworanich and T. Woratanarat). Dr. G Watt provides global oversight in establishing the training and research infrastructure for this site. Office space at PMK and administrative support is currently graciously provided by Dr. Suwicha (Tim) Chitpatima, Director, Office of Special Projects, Royal Thai Army, at PMK.

(iv) B.2 The Site Leader and other Key personnel

Jintanat Ananworanich MD, is the Bangkok Site Leader. Her expertise is described in section (i) E.

Col Sorachai Nitayaphan, MD PhD, is the HACTU Network Leader for HIV Vaccines, and Co-Investigator at the HACTU-Bangkok site. His expertise is also described in section (i) E.

Wichitra Apateerapong RN, MSN, is the Bangkok Site Coordinator. She has over twenty years of experience working as a nurse with various patient populations diverse in age, socioeconomic status, and culture. Ms. Apateerapong has been head nurse of a large medical-surgical service, a position that included management and administration as well as patient care. She was also head nurse for a non-governmental organization (NGO) that provided medical care for refugees on the Thai-Cambodian border. In this position, she not only organized and provided health care, but also interacted with Thai and international public health authorities. She then became Field Coordinator for the same NGO, a position that required increased responsibility and involved planning and implementing programs in curative care, health promotion and disease prevention in an underdeveloped Cambodian province. In 2002, Ms. Apateerapong moved into the research arena. She was a clinical research nurse and project coordinator for HIV-NAT for two years, during which time she supported HIV clinical trials in both children and adults. Her work involved screening and enrolling patients, monitoring protocol compliance and patient well being, HIV counseling and education, and training. She currently coordinates the UH-PMK NeuroAIDS study, managing all aspects of this study including neuropsychological testing. She has a remarkable ability to work independently and to solve problems in difficult settings. She is principal author of 2, and co-author of 10 research abstracts and papers on HIV/AIDS.

LTC Jerome Kim MD, Senior Consultant. See Section (i) E for description

Praphan Phanuphak MD PhD, Senior Consultant. See Section (i) E for description

Thantip Nuchapong, Site Pharmacist, is a trained pharmacist who has supervised pharmacy support for HIV therapeutic trials at HIV-NAT, Thailand's premier HIV clinical trials group. Ms. Nuchapong has received additional training in Good Clinical Practices and will be the lead pharmacist at the Bangkok site through a collaborative agreement with HIV-NAT. Ms Nuchapong will provide oversight over all pharmacy needs, and assure adequate compliance with all local and international laws.

George Watt MD, DTM&H, Co-Investigator, is Associate Professor of Medicine at JABSOM and an Associate Professor of Tropical Medicine at Mahidol University, Bangkok. Dr. Watt has extensive experience in conducting both clinical- and laboratory-based investigations of tropical infections, HIV-1 and of interactions between them. He directs HACRP's operations at PMK/AFRIMS. Dr. Watt is an Associate Editor of the Asian Pacific Journal of Allergy and Immunology and of the Journal of the Medical Association of Thailand, and is first author of more than fifty research publications in peer-reviewed, international medical journals. As Co-Investigator, he will provide clinical care for research participants.

Narongrid Sirisopana MD, Co-Investigator, is currently the Director of the Research Division of AFRIMS. Dr. Narongrid is an internist with additional training in venereal diseases and toxicology. He has considerable experience and expertise in HIV trials and is principal author of several HIV investigations. His expertise in pharmacokinetics will be of use for Phase I/early Phase II trials. As Co-Investigator, he will provide clinical care for research participants.

Mark deSouza PhD, Co-Investigator, is Director, AFRIMS Department of Retrovirology, HIV Clinical Research Laboratory, the only CAP-certified laboratory in Asia. He will provide oversight over the specimen processing/ HIV diagnostics needs of the HACTU-Bangkok Site.

Sataporn Thitvichianlert, MD, MCE, Co-Investigator, is Chief, Division of Infectious Diseases, Department of Medicine, PMK Hospital. He also holds an appointment as an instructor at the PMK College of Medicine. Dr. Thitvichianlert has experience in both HIV-related and non-HIV related clinical trials, and plays a major role in the ongoing UH-PMK NeuroAIDS investigation. Dr. Thitvichianlert is experienced in carrying out investigations in compliance with GCP guidelines. He will assist in the recruitment of and clinical care of HIV seropositive research patients, and act as a liaison with PMK faculty.

Silvia Ratto-Kim PhD, Co-Investigator, is Principal Scientist, Henry M. Jackson Foundation, AFRIMS, Thailand and Associate Researcher at JABSOM. She is currently working at AFRIMS with Dr. Mark deSouza in testing surrogate markers of immunity in the ongoing phase III HIV vaccine trial. In addition, as a member of HACRP, she supervises blood processing, flow cytometry, macrophage culture, retrieval of supernatant and the shipping of specimens for the ongoing UH-PMK NeuroAIDS study. She continues to direct her CD4 Lab at Leahi Hospital as a faculty member of JABSOM.

Thira Woratanarat MD, Co-Investigator, recently resigned his position with the Thai Ministry of Public Health's Division of AIDS to take a position as the Chief, HIV Vaccine Clinical Trials Unit in the Department of Retrovirology, AFRIMS and as Assistant Professor of Medicine with JABSOM, UHM. He directs the Gilead HIV training initiative for civilian physicians in Southeast Asia. He has assisted in establishing the HIV ARV management guidelines for Thailand. He has done post-graduate training at Johns Hopkins School of Public Health and Harvard University in the data analysis of vaccine efficacy trials, research ethics, good clinical practices, and human subjects research education. As a UH faculty member, he will to the science and as needed, in the patient management of research patients for this application.

Other Significant Contributors who have agreed to provide scientific and logistical support for this effort:

Robert M. Paris MD, MPH, Co-Investigator, is an Internist who is Assistant Chief, Department of Retrovirology at AFRIMS. His previous experience as the Chief of the Department of Retrovirology's Vaccine Trials Section and training in Epidemiology at Johns Hopkins School of Public Health and in Preventive Medicine at Walter Reed Army Institute of Research provide unique expertise that should contribute greatly to the work of the Bangkok site.

Carl Mason MD, Co-Investigator, is the current Commander of the US Army Component of AFRIMS and the Chief of its Department of Enteric Diseases. Dr. Mason's infectious disease and public health/epidemiology background is complimented by a previous assignment in the Retrovirology Department, AFRIMS. This gives Dr. Mason a unique expertise in HIV and enteric co-morbidities as well as in study planning, design and execution, and makes him an invaluable asset to the proposed Bangkok Clinical Research site.

Mammen P. Mammen Jr., MD, Co-Investigator, is Chief of the Virology Department, US Army Component of AFRIMS. Dr. Mammen heads a department with 2 facilities in Thailand (Bangkok and Kamphaeng Phet) and a research unit in Nepal. Dr. Mammen is currently PI of a Phase II field efficacy trial of a candidate Hepatitis E Vaccine and of a Phase I/II dengue vaccine trial. His expertise in vaccine development and testing is an additional resource for the Bangkok site.

Mark M. Fukuda MD, Co-Investigator, is the Chief of the Department of Immunology and Medicine, US Army Component of AFRIMS. The main focus of the work of Dr. Fukuda is malaria. Dr. Fukuda and his Department's strong background in biochemistry,

pharmacology and pharmacokinetics add greatly to the proposed Bangkok site, particularly in the areas of translational research and co-morbidities.

Fernando B. Guerena MD, MPH, Co-Investigator, is an Infectious Disease specialist with complementary training in preventive medicine, including 3 years at CDC, Atlanta. He has experience in Thailand working with both HIV-1 and with important co-morbid infections such as malaria.

Samart Nidhinandana MD, Co-Investigator, is a Chief of the Division of Neurology, Department of Medicine at PMK Hospital. Dr. Samart is the co-Principal Investigator in HACRP's UH-PMK NeuroAIDS Study. His expertise would be invaluable for future studies of NeuroAIDS.

Pasiri Sithinamsuwan MD, Co-Investigator, is a staff neurologist in the Division of Neurology, Department of Medicine at PMK Hospital. Dr. Pasiri has played the major clinical role in the ongoing UH-PMK NeuroAIDS study at PMK Hospital.

(iv) B.3 Clinical Trials Infrastructure

Clinical Infrastructure: The proposed clinical trials infrastructure at the HACTU-Bangkok site will build on HACRP's existing clinical research infrastructure at PMK/AFRIMS. Patients will continue to be seen at the RTACRC AFRIMS. Currently supporting the clinical trials needs of Thai AFRIMS's HIV vaccine initiative, this clinic is a fully equipped 1470 square feet facility located on the second floor of the AFRIMS headquarter which includes a reception/waiting area, 2 exam rooms, 3 medical/consent/counseling room and one blood draw/vaccination/treatment room. The clinic is under the direction of Dr. S. Nitayaphan (the proposed Vaccine Leader for this HACTU-Bangkok site).

The administrative offices for the HACTU-Bangkok site will remain within the administrative space of Dr. Suwicha (Tim) Chitpatima, Director of International Affairs for PMK in a building immediately adjacent to the RTACRC AFRIMS. This area is fully equipped with telephone/internet access as well as VTC capabilities. 1400 sq ft of space is available for our staff.

A basic "core" group of personnel for the clinical infrastructure is requested consisting of 2 CRNs, a data manager, a QA/IRB Coordinator, and a half-time recruitment/social worker. Ms. Apateerapong, as the Bangkok Site Coordinator, will coordinate both therapeutic and vaccine clinical trial activities under the supervision of Dr. Ananworanich. She will be responsible for the daily operations, oversee protocol management, interact with the pharmacy and the lab, and supervise the nursing, data management, regulatory and outreach staff. Ms. Prapapron Savaraj, a nurse with more than 4 years experience as a vaccine clinical trials site manager under Dr. Nitayaphan, will assist in the coordination of vaccine trial activities. The nurses may work predominantly either in therapeutics or in vaccines but can be "shared" as needed. A clinical trials structure modeled after the Leahi site structure is envisioned, with the formal framework to include standing meetings (weekly staff meetings and biweekly coordinating committee meetings), creation of SOPs concerning data management, QA, pharmacy and laboratory services. The site recognizes the need for protocol adherence, accurate and timely data transcription, and meticulous quality control. It has many research procedures already in place and is prepared to add to them to ensure patient safety and the production of high quality data. Mandatory training of various personnel in GCP, human subjects, blood-borne pathogen/laboratory safety will be in place. All existing personnel at HIV-NAT and AFRIMS already meet such criteria for training.

Laboratory Infrastructure: Specimen processing, storage and shipment will be managed by the AFRIMS Retrovirology Laboratory under the direction of Dr. M deSouza. This laboratory has extensive experience in regulated clinical trials research

and is familiar with all external proficiency testing requirements. Ms. Apateerapong and laboratory personnel will plan to work together to establish SOPs and maintain open communication to facilitate the smooth interaction between the clinic and the lab and to insure that the laboratory is up to date with the latest protocol amendments.

Pharmacy Management Plan: Pharmacy services will be provided to the Bangkok site as part of a consortium agreement with HIV-NAT to provide space for storage of study medications and to manage all pharmacy-related tasks including importing, purchasing, labeling, dispensing, and maintaining inventory logs, drug accountability information and essential trial-related documents. HIV-NAT is a well-established HIV clinical trials center that has participated in DAIDS clinical studies including Esprit, SMART, STALWART and CIPRA. A Pharmacy Plan for HIV-NAT is in place based on Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks that meets FDA regulations on the use of investigational drugs. The appropriate SOPs will be developed in coordination with the Bangkok site to facilitate study drug transactions between the pharmacy and the site. HIV-NAT is only 2 km away from RTACRC and the pharmacy is located within the main HIV-NAT building. The HIV-NAT pharmacy consists of a climate-controlled room of 35 m^2 for storage of study medications with daily temperature and humidity checks. There are four refrigerators used to study medications requiring refrigeration and sufficient space to secure medication with access limited to pharmacy staff. There is a temperature monitoring alarm system and 24 hour on call pharmacist.

The study nurse at the HACTU-Bangkok site will notify the HIV-NAT pharmacist and send the valid prescriptions with advance notice of the each patient's clinic visit. The pharmacy will prepare the study drug and on the day of the clinic visit, a courier service will transport the study medications according to DAIDS regulations from HIV-NAT to RTACRC clinic. Special temperature controlled boxes will be used to ensure correct temperature during transport. The CRN will take appropriate measures to make certain that the correct medication is obtained and dispensed to the patient. Both the study physician and the CRN will counsel the patient on adherence. The study nurse will send copies of shipment records (between HIV-NAT and the HACTU-Bangkok site) and the drug accountability information to the pharmacist at HIV-NAT to keep on file. Essential trial-related documents will be kept at both HIV-NAT pharmacy and at RTACRC office. Procedures are in place to procure study medication on the study visit day should the need arise. Meetings between the study physician and nurse at the HACTU-Bangkok site and the pharmacist at HIV-NAT will be set to discuss study medication needs for the coming month, issues related to previous month's study medications and any protocol amendments.

Informed Consent Translation and Regulatory Compliance/ Accountability: Within the AFRIMS-PMK system, translations of protocols and informed consent documents are currently being performed by physicians and nurses fluent in English and Thai. Multiple previous attempts to contract out medical translation services in their experience have not produced sufficiently high quality translated documents. The Thai MOPH has recently instituted a requirement that all protocols submitted to their ethical review committee must be translated into Thai. Thus, this grant proposal requests the hire of an individual fluent in medical English and Thai whose primary duties will be to translate protocols, informed consent documents and their amendments from English into Thai and function as a liaison between investigators and IRB officials to assure a smooth running IRB process for each protocol. This Bangkok site IRB officer will also coordinate with Dr. Krai-Rergs, the AFRIMS QA-QC officer who will be responsible for certification of translation and conduct a pre-implementation review of all regulatory documents.

Thailand has a multi-tier ethical review procedure with additional review necessary for HIV related clinical trials and vaccine trials. The primary Institutional Review Board (IRB) will be the Royal Thai Army (RTA) IRB, which has a Federal Wide Assurance from the Office of Human Research Protection in the US (FWA# 00001813). The secondary IRB is likely to be the Thai Ministry of Public Health IRB (OHRP: T-4567; DOD assurance #:;M-20056). The RTA IRB is a primary IRB for Phase I/II HIV vaccine trials, reviews most protocols from AFRIMS, and is the primary IRB for the current Phase III HIV vaccine trial as well as for the UH-PMK NeuroAIDS study. Simultaneously, protocols will also be submitted to the UH IRB for approval. The Bangkok Site will begin screening participants upon written approval from UH and the appropriate Thai IRBs.

Both Dr Ananworanich and Ms. Apateerapong are familiar with clinical trials management and regulatory needs of international protocols and can be depended upon to adapt local logistics to satisfy all regulatory requirements.

Administration/ Fiscal Accountability: Fiscal accountability will be the responsibility of UHM as the organization primarily responsible for the function of the Bangkok site. A full time administrator at the Bangkok site will be recruited to work under Dr. Ananworanich's supervision. He/she will report to Mr. A Lee within our Honolulu office, who will assume administrative and fiscal oversight and assure compliance with all UH, DAIDS and Federal regulations.

Plans for the development of new investigators: The UH-Bangkok site has an unique opportunity to develop new investigators because of the contacts with two Thai Universities (PMK and Chulalongkorn through HIV-NAT's contacts) and one US University (Hawaii). The HACTU-Bangkok site will have the opportunity to be involved in short term or long term HIV care and/or research training of medical students, residents (medicine, pediatrics, OB-GYN, neurology), fellows (infectious diseases, immunology, neurology, others), as well as other potential researchers including statisticians, nurses and medical technologists. It is anticipated that the ID Fellow scheduled to begin his fellowship at PMK will be integrally involved in the UH-Bangkok site HIV research activities. A new 6 week Tropical Medicine/Infectious Disease rotation for internal medicine residents supervised by Dr. G Watt was initiated this year within the JABSOM Internal Medicine Residency Program. HACTU intends to participate in the JABSOM Dept of Medicine's plans to start an ID Fellowship in the Fall of 2006. It is anticipated that such ID Fellows will also rotate through the UH-Bangkok site. An exchange program inviting Thai residents/fellows to train in HIV care/and or research in Honolulu can also be considered.

A complementary grant application will be submitted on August 25, 2005 in response to RFA-TW-03-007: Brain Disorders in the Developing World: Research Across the Lifespan. This application aims to determine Thailand-specific normative neuropsychological data for the cognitive tests must useful in HIV dementia. It will also provide intensive training for an HIV neuropsychologist and an HIV neurologist in Thailand for our programe. In year two of the grant, we intend to estimate the prevalence of cognitive and neurological disorders in Bangkok. Thus, if successful, this complementary application will further develop a critical mass of investigators at our Bangkok site.

(iv) B.4 Site Contribution to Priority Areas

This section describes the past and future protocol participation capabilities of this site. For potential scientific contribution capabilities, see section (ii).

Contribution to the HIV Vaccine Priority Area: AFRIMS (US and Thai) has contributed substantially to the characterization of the Thai HIV epidemic and has figured

prominently in the planning and implementation of the current phase III HIV vaccine trial, which began in September, 2002 in Rayong and Chonburi Provinces east of Bangkok. The Thai-US AFRIMS collaboration has a broad research base; it has collected data on risk factors for HIV infection, done mucosal sampling from HIV infected and vaccinated persons, evaluated chromium release CTL and ELISpot in several hundred vaccine recipients, evaluated NK cell activity and ADCC, and evaluated NAb and T helper responses [1, 4-6, 71-79] HIV vaccine trials have been the main thrust of the research effort of the AFRIMS' HIV research program. The vaccine protocols carried out by AFRIMS have contributed greatly to the body of safety and immunogenicity data on various products [1]. Motivations for volunteering have been analyzed and described [80], and networks for recruiting volunteers have been established in blood donors, monks, naval officers, corporate staff, factory workers, office personnel, attendees at Red Cross Fairs, and word of mouth from previous volunteers. The Division of Research of Thai-AFRIMS, under Dr. Nitayaphan's direction, has accomplished five HIV vaccine projects to date: 1)A Phase I Safety and Immunogenicity Evaluation of BIOCINE HIV SF2 gp120 /MF59 Vaccine in HIV-1 Seronegative Thai Volunteers. 2) Phase I/II, Double-blind, Placebo-controlled Study of the Chiron Vaccines HIV Thai E gp120/ MF59 Vaccine Administered Alone or Combined with the Chiron Vaccines HIV SF2 gp120 Antigen in Healthy HIV-Seronegative Thai Adults; 3) A Phase I/II Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX^{TM} B/E) Boosting in Thai HIV Seronegative Adults. 4) Two booster injections with a higher dose of Chiron Vaccines HIV Thai E gp120 (200 µg)/MF59 Vaccine alone in volunteers previously immunized with Chiron Vaccine HIV Thai E gp120 (100 µg)/MF59 Vaccine or Thai E gp120 (100 µg) + SF2 gp120 (25 or 50 µg)/MF59 Vaccine; 5) A Phase I/II trial of the Merck adenovirus HIV vaccine. In addition, the TAVEG is planning to start 2 new HIV vaccine trials this calendar year. The first is a Phase I test of a new CRF01_AE MVA vaccine and the second an expanded immunologic analysis of the Prime boost combination currently undergoing Phase III testing. With the expertise of Dr. Nitayaphan and his staff, there is no question that the HACTU-Bangkok site has the needed expertise to conduct HIV vaccine trials. There are no other vaccine investigators outside of Thailand and the TAVEG who have the wealth of clinical experience and the broad scientific background of Dr. Nitayaphan. Dr. Nitayaphan has been intimately involved in the design and execution of the current Phase III trial; adding additional practical expertise in Phase III trial execution that would not be found anywhere outside of the TAVEG.

In addition, Dr. J. Kim is now the Chairman of the Executive Committee of the Thai AIDS Vaccine Evaluation Group and is leading the effort to launch the two new Phase I/II HIV clinical trials (MVA and expanded immunologic analysis of the current Phase III Prime boost candidate vaccines). In addition he has helped the Army to develop several new "concept" vaccines – LFn-p24 (a novel vaccine/delivery system using anthrax components to deliver HIV antigens intracellularly), trivalent HIV VEE (Venezuelan Equine Encephalitis), and the MVA-CMDR (subtype CRF01_AE, now undergoing clinical testing). Through his experience with both vaccine-induced cellular immune responses and HIV neutralizing antibody, Dr. Kim should be able to provide both clinical and scientific expertise in the HIV vaccine area (through either the Leahi or Bangkok sites of the HACTU).

Contribution to the Optimization of Clinical Management Priority Area, Including Co-Morbidities

The UH-Bangkok site plans to contribute to research focused on optimization of clinical management to reduce disease progression and minimize co-morbidities. Specifically,

participation is planned in evaluating the effectiveness, safety, durability of response and long-term toxicities of new antiretroviral regimens and in the prevention, control and therapy of co-morbidities. Dr. Ananworanich has had substantial experience in clinical trials management of studies dealing with optimization of HIV care. She has been the project leader in Thailand for the Staccato study, one of the largest structured treatment interruption (STI) of highly active antiretroviral therapy (HAART) studies with over 400 patients in Thailand which will conclude in October of 2005 as well as a separate HIV-NAT initiated STI study [81, 82]. She has published on the incidence and risk of rash following Nevirapine or Efavirenz or combination therapy [83]. The sophisticated clinical and laboratory support of AFRIMS will allow the Bangkok site to participate fully in optimization trials that may require stringent laboratory and pharmacokinetic capabilities. Dr. Ananworanich has led several pharmacokinetic studies in adults and in children [84-86]. Dr. Ananworanich has also led studies evaluating resistance in children and adults [87, 88].

The laboratories at AFRIMS will provide a tremendous basic science and translational resource for co-morbidity studies. These laboratories will be able to offer specialized assays that may be important in co-morbidity trials. AFRIMS has conducted several trials investigating HIV and co-infections, including malaria, dengue, and scrub typhus [89, 90]. Important causes of co-morbidity in Asia, such as penicilliosis, have also been investigated by AFRIMS [91]. HCV co-infection have been evaluated by the Retrovirology Department as a marker for HIV mode of transmission [63, 92]. Hepatitis has long been a major area of emphasis for the Department of Virology and AFRIMS and, in addition to HCV, co-morbidity of HIV with hepatitis viruses B and E is of serious concern in Southeast Asia. Hepatitis A vaccine was originally field tested at AFRIMS, and PCR assays are available at AFRIMS for hepatitis A, B, C, E and G. AFRIMS has played a leading role in describing hepatitis E (HEV) disease, obtaining virus strains for genetic characterization and developing and evaluating diagnostic tests to detect infection. A vaccine trial against HEV is currently underway.

(iv) B.5. Recruitment and Retention

Recruitment Strategies

HIV Seronegative Subjects for HIV Vaccine Trials: Dr. Nitayaphan and his colleagues are very familiar with the demographics of the population in the Bangkok region. For the minimum 20 participants on trial/month, it is envisioned that their standard recruitment SOP will be sufficient for accrual and will likely exceed these minimal requirements. As AFRIMS has a long-tract record of collaboration with multiple partners including the CDC and NGOs in the region, target recruitment of specific high risk groups should also be possible.

HIV Seropositive Subjects for Therapeutic Trials: The primary location of recruitment for HIV seropositive subjects will be the PMK ID Clinic. Currently, PMK's ID Clinic has limited its clinic to 500 HIV infected subjects due to physician resource constraints. However the ID Clinic intends to expand its physician capability especially in view of the anticipated ID Fellow this year and may accept more HIV patients. In any case the potential far exceeds the required enrollment of 20 subjects on study/month. Many of our NeuroAIDS study participants were referred from outside sources through word-of-mouth, suggesting that recruitment from sources outside of PMK will not be problematic. The Bangkok CAB will also be expected to offer assistance and recommendations regarding recruitment strategies and work with the site to develop an effective recruitment plan.

Retention Strategies: We believe that individualized and personalized care of each patient, assisting with their medical care and providing the resources necessary to enable their participation in clinical trials are key to good retention. There have been no lost to follow-up among the 36 subjects enrolled within the UH-PMK NeuroAIDS study. TAVEG has traditionally not had difficulty retaining its HIV vaccine volunteers, with >95% completing the study. The following are strategies that will be considered for implementation at the HACTU-Bangkok site particularly for HIV seropositive patients: 1) Safety labs and medical issues identified at each study visit will be forwarded to the primary physician/clinic of record for use in their routine medical care. 2) Patient volunteers and their families will have 24 hour access to the study team by phone. 3) Patients will be compensated for loss of income if they must miss work to participate in any study visit and will be reimbursed for transportation to and from clinical visits. 4) Child care costs will be taken care of as necessary. 5) The budget for the UH-Bangkok site incorporates a part-time social worker who can assist with obtaining antiretroviral medications for patients (such as through the Division of AIDS of the Thai Ministry of Public Health and the Bangkok Metropolitan Association [BMA] AIDS Center in Chonburi), temporary living quarters (Mercy Center for HIV-infected women), transportation and family support for HIV-infected individuals (AIDS Care Education and Training [ACET]) and substance abuse treatment (Rajayithi Clinic for Drug Abuse).

Ability to initiate enrollment within 6 months of funding: The proposed Clinic, Lab and Pharmacy are already staffed and functional. Much of the problematic areas and logistical issues have been resolved with the initiation of the pilot NeuroAIDS study. Therefore there are no major concerns regarding the ability to initiate enrollment in a timely fashion within 6 months.

Plan and capabilities to meet a capacity requirement of an average of 100 study participants over a 12-month period for each Network

HIV Seronegative Subjects for HIV Vaccine Trials Participant enrollment to an average of 100 /month is not anticipated to be a problem for this site. This is based on our established relationships and contacts particularly through investigators at AFRIMS who have a long track record of careful epidemiologic surveys and track record for recruitment of HIV seronegative subjects for HIV Vaccine Trials. It is envisioned that the method of recruitment will vary by the specific cohort that is desired. For example, for the MSM population, AFRIMS has contacts both with the CDC who has been studying MSM cohorts in Bangkok and with the Rainbow Sky Organization (an MSM NGO in Bangkok) which may facilitate access to this population.

Increasing the clinical trials infrastructure to allow for a capacity of 100 study participants/month is also felt to be feasible. Dr. Nitayaphan has several CRNs at the RTACRC responsible for other clinical trials that can be assessed to assist on a temporary basis until more staff can be hired.

HIV Seropositive Subjects for Therapeutic Trials It is anticipated that increasing capacity to an average of 100 study participants over a 12-month period at the UH-Bangkok site will be possible. AFRIMS has had considerable experience recruiting HIV infected persons from the area around PMK hospital in an HIV natural history study that ran for 5 years. During the Phase I/II HIV vaccine trials at AFRIMS, our clinical research coordinators developed extensive ties with community groups and NGOs (most representing PLWHA). The HIV Clinic at PMK currently has over 500 patients and an active HIV inpatient service. Further access to patients can be secured through various contacts of our program investigators with other AIDS providers in the general Bangkok region. Many of these contacts have already been made to secure appropriate HIV clinic settings for the training of our SE Asia physicians. Clinics/organizations with whom

we have an existing working relationship and that might be asked for accrual assistance or perhaps subsite establishment would include Bamrasnaradura Institute with an 48,700 outpatient visits/year by HIV infected patients, and Chonburi Regional Hospital with an HIV outpatient clinic of 3000 patients.

Institutional/organizational support for the conduct of clinical research under U.S regulations: By U.S. Army regulation, all clinical trials conducted at AFRIMS by US and Thai investigators must comply with all applicable US Army and US government regulations. All investigators and nurses are trained in GCP and all have taken ethical training. The MOPH and RTA IRBs have FWA numbers. The US Army HSRRB (IRB) also abides by all US regulatory requirements. HIV vaccine research at AFRIMS has been monitored by the Henry M. Jackson foundation, Chiron Corporation, and Phyllis Kent (an independent auditing firm). The current Phase III trial is being monitored by Quintiles and the Clinical Trials Monitoring Branch of the U.S. Army Medical Materiel Development Activity.

Facility assurance during natural disasters and power failure: The AFRIMS facility is supported by a full-time back-up generator for unexpected power failures. This is the site of storage for study specimens. PMK hospital, the site of the administrative offices is also supported by a generator. Neither building is in a high-risk area for natural disasters and was completely spared from the devastating effects of the recent tsunami.

(iv) B.6 Plans for Community Involvement

Community Advisory Board (CAB): Community involvement is an integral component of a successful clinical trials structure and HACTU is committed to a CAB that functions as the "voice" of the local community from which it draws its participants. Similar to the Leahi Site CAB, it is anticipated that this CAB will function to review protocols for applicability to the local population, provide input regarding research prioritization, identify barriers to research participation, provide assistance with outreach and recruitment and provide representation from the local community to the DAIDS Network level. Initially CAB services will be provided to the UH-Bangkok site as part of a consortium agreement with HIV-NAT as no CAB exists at PMK/AFRIMS. However, as HIV-NAT's CAB is structured to serve a larger community representation purpose with planned representation from multiple clinical sites under their proposed Clinical Trials Unit and to include participation not only from HIV-infected patients but from leaders from various NGO and Societies, it is envisioned that a more "local" UH-Bangkok – specific CAB will be warranted if funding is secured. Creation of such a CAB is planned in the first year of funding. It is also envisioned that a representative of our UH-Bangkok CAB would then be sent to the HIV-NAT CAB to represent our site.

Community Outreach: With the assistance of the local CAB, the UH-Bangkok site will start a process of becoming a resource for the community that supports its research. One of the tasks of the initial year will be in identifying community and hospital partners for such partnership. Much will depend on the need assessment of the community but It is envisioned that community outreach might begin with a series of basic community lectures on HIV prevention, role of vaccines and HIV care and treatment given by our physicians perhaps initially targeting the patients that come for outpatient care at PMK.

e. Human Subjects Research and Protection from Risk

Targeted/Planned Enrollment Table is attached for the following:
Leahi Clinical Research Site:

- ACTG Network

- HIV Vaccine Priority Area
- Microbicides Priority Area
- ACTG Transitional Subjects

Bangkok Clinical Research Site:

- Optimization of Care Priority Area
- HIV Vaccine Priority Area

Protection of Human Subjects

Leahi Clinical Research Site:

The proposed principal investigator is in compliance with the Office for Human Research Protection (OHRP) requirement concerning protection of human research participants and has taken the NIH-sponsored course (Certificate Serial # 969752241; September 23, 2000) on this topic. All personnel working on this project will undergo training in the protection of human research participants.

Risks to the Subjects:

Human Subjects Involvement and Characteristics: This study proposes clinical research involving human subjects who are HIV-1 infected and non-infected. Male and female adult and adolescents will be recruited. Except as mandated by protocol requirements, individuals will not be excluded from participation on the basis of sex or ethnicity.

Sources of Materials: Blood and other samples will be obtained from the study subjects. All data and material will be obtained specifically for research purposes although routine laboratory data obtained as part of the study will be forwarded, with the subject's consent, to his/her primary physician so that it may be utilized for routine medical care. The patient will be asked for consent to obtain necessary outside records such as records from his/her private physician should such information be needed for the purposes of this study.

Potential Risks: Participation in this study may carry a risk of loss of confidentiality with associated psychological, social or legal risks. Steps will be taken to minimize this risk as explained below. Other risks may be apply depending on the protocol involved

Adequacy of Protection against Risks:

Recruitment and Informed Consent: The majority of the recruitment is anticipated to come from referrals from community physicians, community clinics, our community advisory board members or from the AIDS service organizations. Upon a telephone query from a potential participant, an appointment for a screening visit will be made. The research nurse/associate assigned to this study will explain the study and answer any questions. The subject will be asked to read the informed consent document. After obtaining the consent, study-specific screening will be conducted. Prior to entry, the subject will have an opportunity to discuss the study with the principal investigator or other physician co-investigators and have any remaining questions answered.

Protection against Risk: Hawaii AIDS Clinical Research Program standard operating procedures are designed to minimize potential risks and contain specific provisions for use in the event of adverse effects. Case report forms (CRF) will be kept for each subject. Subjects will not be identified by name on any study document leaving our research program. Subjects will be identified by the study's patient identification number (PID) on all requests for blood tests or procedures. All documents will be held to strict confidential procedures and stored in double locked facilities. All documents, which

identify patients by name, will be stored separately from case report forms and access to records will be limited to personnel required for the conduct of the research. Confidentiality will be maintained through all phases, including data analysis and publications. In the event of adverse effects to the subjects, the HACRP physician researchers are available to provide necessary medical care although the financial responsibility for hospitalization and other necessary care will be the responsibility of the subject.

Potential benefits of the proposed research to the subjects and others
There may be no major benefit directly to the participants of the study. The potential benefit of the proposed study is the medical knowledge that can be gained from this study

Importance of the knowledge to be gained
Results of studies may extend our knowledge of how HIV or its complications may be prevented or treated.

Inclusion of Women
Except as mandated by protocol requirements, subjects will not be discriminated on the basis of gender.

Inclusion of Minorities
Individuals will not be excluded from participation on the basis of ethnicity**.**

Inclusion of Children
Depending on protocol requirements, children (adolescents age 13 and older) may be enrolled into studies.

Bangkok Clinical Research Site:
Dr. Ananworanich and all other personnel working on this project will undergo training in the protection of human research participants.

Risks to the Subjects:
Human Subjects Involvement and Characteristics: This study proposes clinical research involving human subjects who are HIV-1 infected and non-infected. Male and female adult and adolescents will be recruited. Except as mandated by protocol requirements individuals will not be excluded from participation on the basis of sex or ethnicity.

Sources of Materials: Blood and tissue samples may be obtained from the study subjects. All data and material will be obtained specifically for research purposes although routine laboratory data obtained as part of the study may be forwarded, with the subject's consent, to his/her primary physician so that it may be utilized for routine medical care. The patient will be asked for consent to obtain necessary outside records such as records from his/her private physician should such information be needed for the purposes of this study.

Potential Risks: Participation in this study may carry a risk of loss of confidentiality with associated psychological, social or legal risks. Steps will be taken to minimize this risk as explained below. Other risks may be apply depending on the protocol involved

Adequacy of Protection against Risks:

Recruitment and Informed Consent: Upon a telephone query from a potential participant, an appointment for a screening visit will be made. The research nurse/associate assigned to this study will explain the study and answer any questions. The subject will be asked to read the informed consent document. After obtaining the consent, study-specific screening will be conducted. Prior to entry, the subject will have an opportunity to discuss the study with the principal investigator or other physician co-investigators and have any remaining questions answered.

Protection against Risk: Hawaii AIDS Clinical Research Program standard operating procedures are designed to minimize potential risks and contain specific provisions for use in the event of adverse effects. Case report forms (CRF) will be kept for each subject. Subjects will not be identified by name on any study document leaving our research program. Subjects will be identified by the study's patient identification number (PID) on all requests for blood tests or procedures. All documents will be held to strict confidential procedures and stored in double locked facilities. All documents, which identify patients by name, will be stored separately from case report forms and access to records will be limited to personnel required for the conduct of the research. In the event of adverse effects to the subjects, physician researchers are available to provide necessary medical care although the financial responsibility for hospitalization and other necessary care will be the responsibility of the subject.

Potential benefits of the proposed research to the subjects and others

There may be no major benefit directly to the participants of the study. The potential benefit of the proposed study is the medical knowledge that can be gained from this study

Importance of the knowledge to be gained

Results of studies may extend our knowledge of how HIV or its complications may be prevented or treated.

Inclusion of Women

Except as mandated by protocol requirements, subjects will not be discriminated on the basis of gender.

Inclusion of Minorities

It is envisioned that all participants will be native Thai. However, individuals will not be excluded from participation on the basis of ethnicity**.**

Inclusion of Children

Depending on protocol requirements, children (adolescents age 13 and older) may be enrolled into studies.

f. Vertebrate animals (not applicable)

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h. Consortium and Contractual Agreements

ACTG Letter of Affiliation

Thai AFRIMS

Henry M. Jackson (US AFRIMS)

HIV-NAT

Queen's Medical Center

B-1-APMMC Hanoi May 9-13, 2005, Agenda (Simulation and Training)

APMMC Hanoi – May 9-13, 2005

Agenda – Simulation Training, Trauma Life Support, May 9-11, 2004

Day 1: Simulation and Training I, May 9th, 90 minutes, 1:30-3:00 PM
Lawrence Burgess, MD, Moderator

Simulation Training Overview 15 min Lawrence Burgess, MD

- Training landscape and problems: no dollars, personnel, must build curriculum, etc..,
- Proposed solutions: local approaches; enterprise approaches
- Reviews types of training: (mannequins: part vs. full task trainers, immersive virtual reality.
- Difference of cognitive vs. procedural (gross motor and/or fine motor) vs. integrated types like mannequin for gross motor or immersive virtual reality for fine motor
- Intro: More than just training, must have curriculum, back end for data collection.

Overview of Tools for Training: Cognitive and Integrative Training through both Computer-based and Mannequin-based trainers 35 min Alan Morgan, MD speaker

- Cognitive training through MicroSim
- Integrated training through SimMan

Overview: Comprehensive Approach to Simulation Training
35 min John Schaefer, MD

- Focus on aspects of the pie chart for systematic approach to training including center, curriculum, evaluation, or ie, the training aspect is only one aspect.

Q&A 5 min

Day 2 Simulation and Training II, May 10th, 90 minutes, 10:30am –12:00noon
Lawrence Burgess, MD, Moderator

Military Medical Integrative Training 35 min Alan Morgan, MD

- Discuss how MicroSim and SimMan are actively being used in the US and abroad to train a wide range of military health care providers from medics to nurses to physicians.

WISER System for Simulation and Training
35 min John Schaefer, MD

- Discuss the on-line curriculum, pretest, scenario, center issues, developing directors, facilitators, costs, etc.

SimMan DEMO – Bleeding Module	20 min	Schaefer, Morgan, Whitford
Q&A	5 min	

Day 2 Military Simulation Working Group Panel, Open Working Luncheon Meeting, 1200 Noon- 1:30pm
Chair and Moderator: Lawrence Burgess, MD
Panelists: 7 minutes per talk
Scott Gilstrap, UPMC – Government Funding to initiate Simulation program
Robert Hardie, UPMC- Business development for self-sustainment
LTC Skip Whitford – Simulation training for the military; challenges in implementation
Alan Morgan- Grand scheme for military deployment
Phil White- Next steps for Asia-Pacific working group
- Other training courses in Asia?
Open Discussion

Day 3 Simulation and Training III, May 11th, 4.5 hours
Lawrence Burgess, MD, Moderator

Cont. Breakfast	0700-0730

Opening remarks: separation into 4 groups and rooms 0730-0745
Scenarios 1-4 divided in groups of 10, rotating between 4 stations in 4 different rooms (including computer room).

-MicroSim (print certificates)	Laerdal representative
-Pre-hospital	LTC Skip Whitford
-ATLS type scenario	Alan Morgan
-ACLS type scenario	John Schaefer

Scenario 1 0745-0900
15 minute introduction to scenario and training goals
1 hour of multiple sessions with individuals rotating
Scenario 2 0900-1015
15 minute introduction to scenario and training goals
1 hour of multiple sessions with individuals rotating

Break	1015-1030
Scenario 3	1030-1145
Scenario 4	1145-1300
Conclusion, Certificates	1300

B-2 – Abstract for APMMC Simulation Training

Abstract Format and Submission Guidelines

1. Abstracts may be submitted for platform or poster presentations.
2. Submission deadline is 14 February 2005.
3. Please register for the conference before submitting an abstract.
4. Send us this information about your presentation (On line, e-mail or fax.):
    - **Name of person submitting: Lawrence Burgess**
    - **Name of presenter: Lawrence Burgess**
    - **Country: USA**
    - **Your preference:** presentation only
    - **Your format:** lecture/slides as part of Simulation Workshop
    - **Your requirements:** PowerPoint
    - **Address these questions:**
      Is your presentation part of a "package" of presentations? Yes, part of Simulation Workshop
      Is more than one person speaking during your presentation? No
5. Abstract guidelines
    - Maximum of 350 words
    - Microsoft Word document, 12 point Times New Roman
    - Title: ALL CAPS, BOLD
    - Author: Given Name (first name) Surname (last name), Title, Service, Assignment
    - Abstract: Spell out all abbreviations at least once.

Simulation Training Overview

Simulation may consist of training to test cognitive skills or procedural skills, or combine both in an integrated format. Simulation environments can be either physical such as using computerized mannequins, or virtual where a computerized, virtual environment simulates the real world. This session will provide a broad overview of these concepts, so that appropriate training environments can be selected by course directors for students depending on the desired outcomes of training. The pros and cons of each type of training will also be reviewed. Ideally, integrated training assists in reducing the "deer-in-the-headlights" look of young health care providers as they transition from books to live patients and scenarios. In addition, advanced simulation technologies permit the study and practice of disease states that may not be seen in every day practice. This is particularly applicable to military health care, in which trauma is not routinely managed by the vast number of providers being deployed. With these advanced computerized training tools, scenarios can be tailored to the specific needs of the trainees.

Advanced Simulation Training: Hands-On Session

Simulation can be conducted using both computer-based modules and computerized mannequins. Hands-on familiarization with the capability of these advanced training tools will lead to better acceptance and understanding of this technology. Such training can improve both initial training while maintaining skills for those outside of formal

training programs. In this session, hands-on familiarization will be conducted at four stations. Participants will have 75 minutes at each station. Laerdal computerized mannequins will be utilized for three topic areas: pre-hospital, trauma life support, cardiac life support. The fourth station will look at a computer-based modules through Laerdal's MicroSim Product. Paricipant's will receive a certificate of completion for this training session.

B-3 – International Military Medical Simulation Symposium After Action Report

International Military Medical Simulation Symposium

9-11 May, 2005

Asia Pacific Military Medicine Conference XV
Melia Hotel, Hanoi Vietnam

AFTER ACTION REPORT

14 June 2005

Prepared by:
COL Benjamin W Berg
APMMC XV Scientific Program Coordinator

OVERVIEW

The Asia Pacific Military Medicine Conference (APMMC) is a US Army Pacific (USARPAC) program conducted in support of the Pacific Command (PACOM) Theater Security Cooperation Plan (TSCP). The conference engages 25-30 Asia-Pacific international Military Medical departments in a program of scientific exchange during a 5 day conference. APMMC has been conducted annually for 15 years. Topics presented by delegates are of general interest with a focus on operational medicine, military medical technology, disaster relief and humanitarian assistance, infections disease, HIV, and environmental medicine. Over 200 presentations are made during this English language conference.

Simulation training techniques are an integral component of US Army Medic programs. Advanced simulation education systems are facilitating broader use of simulation training across a broad spectrum of medical disciplines. Simulation training represents an opportunity to engage across language and cultural barriers and to enhance international medical education activities. Transcultural simulator based education remains unexplored, and is required to effectively integrate successful US based educational strategies for international educational programs.

The Simulation symposium was comprised of two didactic sessions including real-time demonstration simulator orientation, and a one-day simulation hands-on practicum, focused on provision of simulation experience to the co-hosting Vietnamese Army medical personnel. English to Vietnamese translated written documents including medications, and scenario algorithms were utilized for the simulation practicum.

Inclusion of a simulation symposium on the APMMC XV program was made possible through cooperation of US universities, the USARPAC, the Peoples Army of Vietnam (PAVN), Laerdal Inc. Asia, and Laerdal Inc. US, and the Henry M Jackson Foundation. Continuing Medical Education credits (10 credit hours) were provided through the US Army Office of the Surgeon General.

FACULTY AND KEY CONTACTS

University of Pittsburgh Medical Center
Winter Institute for Simulation and Educational Research (WISER)
FACULTY
John Schaeffer, MD
Mr. John Lutz

University of Hawaii, John A. Burns School of Medicine
Telehealth Research Institute
Simulation Course Director, FACULTY
Lawrence Burgess, MD

University of Texas, San Antonio
FACULTY
Alan Morgan, MD

Army Medical Department Center and School
US Army Combat Medic training
FACULTY
LTC Alan Whitford (MD)

Tripler Army Medical Center
APMMC XV Staff
PROGRAM COORDINATION
COL Dale S Vincent, MD
LTC Joseph Pina, MD
COL Benjamin W Berg, MD

Laerdal Inc.
COMMERCIAL SPONSOR
TECHNICAL SUPPORT/MANNEQUIN PROVISION
Ms. SK Lim Lee - Laerdal Asia
Mr. John Rogers - Laerdal USA

Henry M Jackson Foundation
COMMERCIAL SPONSOR COORDINATION
Ms. Kristee Killpack

PROGRAM

May 9th: 1330-1500
Simulation and Training I

Simulation Training Overview	***L. Burgess, MD***
Overview of Tools for Training:	
Cognitive and Integrative Training with	
MicroSim and SimMan	***Alan Morgan, MD***
Overview: WISER Approach to Simulation Training	***John Schaefer, MD***

May 10th: 1030-1300
Simulation and Training II

Military Medical Integrative Training	***LTC Whitford, MD***
WISER System for Simulation and Training	***John Schaefer, MD***
SimMan DEMO -	***John Schaefer, MD***
Military Medicine Simulation Working Group	***LTC Whitford, MD***

Wednesday, May 11th: 0700-1300
Simulation and Training III – Simulator Practicum

Opening Remarks ***L. Burgess, MD***

Scenario 1-MicroSim - Mr. Rogers
Scenario 2-Pre-hospital - Dr. Whitford
Scenario 3-ATLS - Dr. Morgan
Scenario 4-ACLS - Dr. Schaeffer

ATTENDEES

Lecture Series:

Open sessions with no roster maintained. Room configured to accommodate 60 attendees was filled with standing-room-only attendees during both sessions. Sessions were attended by General Officers from the US, India, Malaysia, Vietnam, Australia, Cambodia, Laos, Singapore, Thailand, and other nations. Surgeons General from multiple nations attended.

Simulator Practicum:

This session was constructed primarily for pre-registered Vietnamese participants. Several other nations were represented as permitted by a space available sign up roster.

Vietnam – 38 Participants.
Medical students, physicians in training, senior critical care specialists, surgeons, and anesthesiologists participated.
US – 4 Military Medical Officers
Korea – 2 Military Medical Officers
Malaysia – 2 Military Medical Officers

SUMMARY

Simulation didactic sessions were well attended, exceeding attendance expectations and capacity of the facilities. The integrated presentations from academic and military programs provided a broad overview of simulation training, military relevance, and technical capability. Attendees engaged the faculty in discussion. Significant interest in development and/or enhancement of simulator training capacity was expressed by senior medical officers from Australia, Singapore, Vietnam, India, and Thailand. Simulation based medical education concepts across multiple domains were presented. Cognitive-behavioral learning concepts, technical details, logistics, and faculty development were included in the two days of didactic presentations.

Demonstration mannequin systems were utilized in several of the presentations. Minor technical problems prohibited demonstration of mannequin system features on one occasion, but did not significantly impact the presentation of important concepts or capabilities.

Simulation Practicum sessions were conducted utilizing standard US based training scenarios. The mannequin technical systems were flawless. Vietnamese participants were selected by the host nation for English language skills and the most capable participants served as translators for the scenarios in their own groups. However, for future programs, we will have a translator for each working group designated beforehand. Participants ranged from senior clinical faculty in critical care and anesthesia to second year medical students. Most participants were familiar with the basic clinical concepts presented; none had previous simulator experience. These sessions included rotations through three mannequin based scenario stations and one computer-based simulation program, Micro-Sim®. The practicum sessions were the highlight of the program. The sessions facilitated direct and substantive student-teacher interaction. This type of direct interaction within the context of medical problem-solving and simulated procedures was entirely novel for participants. The educational processes, which were demonstrated, were enthusiastically received by all participants. Program coordinators observed active participant engagement across all domains of the program, including cognitive, skill development, and transcultural adaptive attitudes. Students enthusiastically accepted Certificates of Participation at the conclusion of the program.

In Vietnam the director of the 103 Military Hospital recalled the Director of the Military Medical Academy to review the simulation program. This high level review resulted in a specific request to consider simulation training in future US/Vietnam Military to Military programs.

CONCLUSIONS

1. Introductory simulation training and demonstration based on an American model of education effectively engaged Vietnamese and other non-US participants who have different cultural, language, and medical experiences.

2. Senior medical leaders in the Asia Pacific region view medical simulation training as a method with potential for integration with existing regional military training programs.

3. Simulation training represents a novel method of transcultural medical education that should be explored and expanded.

4. This educational program effectively leveraged academic, military, and industry resources to execute a program within a program.

RECOMMENDATIONS

1. Effective translational processes to maintain the basic integrity of the educational content using modifications that address the unique features of international settings and cultural preferences require further definition.

2. APMMC XVI, Delhi India should include a Simulation Symposium modeled on the APMMC XV (Hanoi, Vietnam) program.

3. International educational simulation programs should include formal student and faculty feedback focused on cultural, language, and medical contextual factors to adapt existing American educational processes to regional military medical communities.